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SOME CHALLENGING ASPECTS OF HEMOGLOBIN METABOLISM *

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MAY I say, Mr. President, that the honor of the John Phillips Lectureship of this College conveys mingled feelings of gratification and humility, much enhanced by contemplating the list of distinguished men who have preceded me on the 20 occasions that this lecture in memory of Dr. Phillips has been given. I sincerely acknowledge my appreciation of this great privilege.

The work from our laboratory which I shall have occasion to mention was accomplished only through the generous effort of many associates at one time or another in the last 25 years. I shall strive to represent faithfully their important contributions.

The title I have chosen is somewhat misleading in respect to the word "hemoglobin." As you are aware, globin constitutes 96% of the molecule, yet I shall confine my remarks to compounds related to the heme fraction. Though but 4% of the molecule, this is largely responsible for its red color and its physiologic function.

In the time at my disposal I should like to present a brief contrasting survey of certain anabolic and catabolic aspects of heme metabolism.† These

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† Historical aspects are considered in more detail in the author's E. T. Bell Lecture,[1] which also includes certain topics pertaining to the general theme that are not included here. At the same time, the present discussion attempts to bring up to date some questions which were raised in the Bell Lecture.

terms are employed arbitrarily, with heme itself as the apex of anabolic activity, regardless of whether it is incorporated in hemoglobin and erythrocyte.

A student of this subject ought to hold color in high esteem. One of the compensations of the necessarily laborious and—some think—even unesthetic work on feces, bile and urine so essential to studies in this field, is the derivation of many beautifully colored compounds. By chromatographic and other fractional methods a striking array is often obtained and I think will be apparent as we proceed.

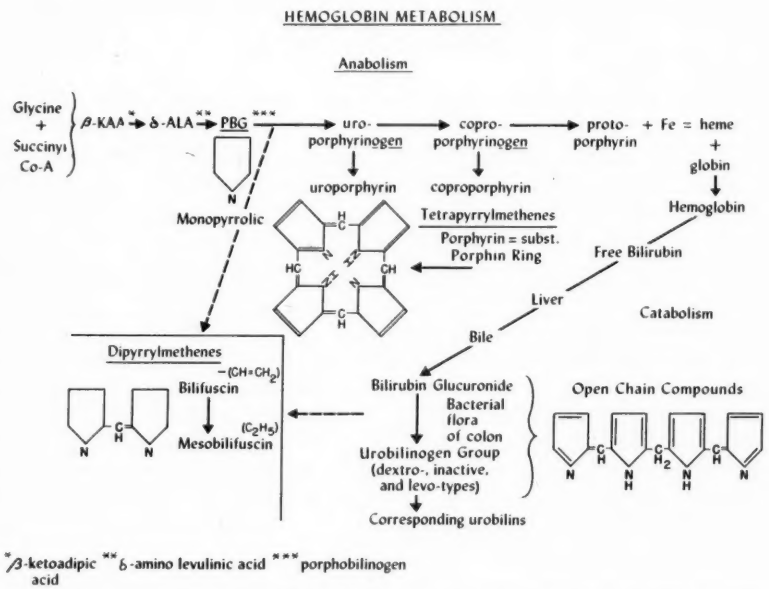

FIG. 1. A skeleton outline of hemoglobin metabolism (see text for details and discussion of dipyrrylmethene group).

In this field of study we are concerned with the truly primeval and almost ubiquitous pyrrol nucleus, occurring either singly, in pairs, or in fours. In the skeleton outline of hemoglobin metabolism shown in figure 1 the anabolic sequences are represented by the monopyrrolic compound, porphobilinogen, (PBG), and by the porphin ring—four pyrrol nuclei connected by CH, or methene bridges. This is basic to all the porphyrins, including that of the hemoglobin molecule. As I shall mention later, it is not unlikely that tripyrryl compounds are intermediary between PBG and the porphyrins. The catabolic sequences are those of the bilirubinoids or bile pigments, tetrapyrrylmethene chains rather than rings. I shall refer to these again in a few moments. In figure 1 the broken line arrows to the "fuscin" group,

or dipyrrylmethenes, indicate their possible derivation from either anabolic or catabolic sources. I shall discuss new evidence * that the former are much more important, although it is recognized that under appropriate circumstances the bilirubinoids may be split in half to yield dipyrryl compounds. In this connection I might point out now that the method we have employed * in measuring the dipyrrylmethene group separates most of the bilirubinoids at an early stage, in order to minimize artefactual conversion to the fuscin compounds.

The monopyrrolic porphobilinogen, though normally not in evidence, has recently become recognized as the center of the anabolic pathway to heme (figure 1), not merely a manifestation peculiar to the relatively rare disease, acute porphyria. I shall not consider the steps in the biosynthesis of porphobilinogen from glycine and succinate, which have been clarified by the brilliant studies of Shemin and his co-workers [2, 3, 4] in New York, Westall,[5] Cookson and Rimington,[6, 7] and Neuberger and Scott [8] in England.

I wish to emphasize the significance of the colorless, nonfluorescing porphyrinogens in the anabolic pathway. Some years ago we [9] pointed out that these compounds were regularly demonstrable in the excreta and easily converted by ultraviolet light or iodine to their respective porphyrins, which are red and exhibit intense red fluorescence in ultraviolet light. Recent studies by Neve and associates,[10] and in this laboratory with Dr. Bashour and Dr. Schwartz,[11] have shown that the biosynthesis of heme is accomplished over these porphyrinogens, and that the porphyrins themselves are by-products (figure 1). It remains to be determined whether a protoporphyrinogen is essential to the final fabrication of the heme molecule.

For many years it was widely held that the porphyrins of the excreta were hemoglobin derivatives—in other words, of catabolic origin. As discussed in more detail elsewhere,[12] it was shown some 20 years ago that the coproporphyrin in hemolytic jaundice and pernicious anemia, as well as in the normal state, is mainly type I isomer, differing in configuration from the type III porphyrin of the hemoglobin molecule. This clearly pointed to an anabolic significance. Later, in a study with Grinstein,[13] it was shown that even where type III porphyrin is excreted in great excess, as in lead poisoning, it is anabolic rather than catabolic in character. The use of isotope labeling has been of decisive value in obtaining such evidence, in both lead poisoning and porphyria.[14, 15, 16] A striking example was afforded in a study with Lowry and Hawkinson,[17] using Shemin's method of feeding N^{15} glycine.[2] This showed early incorporation of N^{15} in the porphyrins, but none at the time of destruction of mature erythrocytes at 120 days, clearly indicated by a second peak in the fecal stercobilin and the rapid decline of N^{15} in the circulating heme. The basis of the early N^{15} peak in stercobilin, first observed by London and co-workers,[18] will be discussed subsequently.

* With Dr. Gilbertsen, Dr. Lowry and Miss Hawkinson, to be published.

I wish to turn now to the catabolic aspects of heme metabolism, especially the urobilinogen problem and the question of significance of the dipyrrylmethenes. Figure 2 shows the principal derivatives of heme catabolism, i.e., the tetrapyrrylmethene bilirubinoids, as mentioned at the outset. The main line of transition here is indicated by the vertical arrows. The principal events are the conversion of hemoglobin to bilirubin,[1] and its reduction to the colorless urobilinogens, a group to which I shall return in a moment. With the exception of the colorless d-urobilinogen, all of the compounds to the left of the vertical pathway are by-products or chemical artefacts; nevertheless, they are often of importance in identification, as I shall point out a

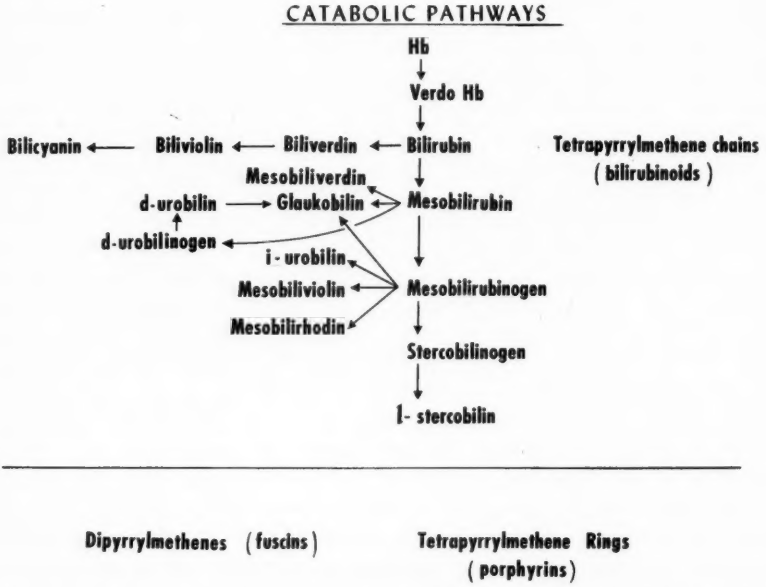

FIG. 2. The principal derivatives of heme catabolism are shown above the horizontal line, the main pathway being indicated by the vertical arrows. In the text, evidence is discussed as to the anabolic significance of the fuscin and porphyrin groups.

little later. The horizontal line merely serves to reëmphasize that the bilirubinoids or tetrapyrrylmethene chains are mainly catabolic, while the porphyrins, or tetrapyrrylmethene rings and the fuscin group of dipyrrylmethenes, are more important from an anabolic standpoint. It is of interest that the color of normal feces is thus dependent on both catabolic and anabolic sequences, being due to a mixture of bilirubinoids, chiefly stercobilin, and compounds of the fuscin category.

As noted in figure 3, the isolation of the three types of crystalline urobilin [19, 20, 21] has made it clear that the term "urobilin" applies to a group of closely similar orange-yellow compounds exhibiting green fluorescence with

zinc. Although not isomers, the three forms are conveniently designated as d-, i- and l- on the basis of their truly remarkable differences in optical activity, as indicated. Each is derived from its respective colorless chromogen or urobilinogen by loss of two hydrogens. The pathway of bacterial reduction in vivo is one of increasing hydrogenation from d- to l-, as shown.

As discussed in more detail elsewhere,[1, 21c] d-urobilinogen and dihydromesobilirubin are isomers ($C_{33}H_{42}N_4O_6$). Although the former has been encountered under apparently normal circumstances, it is not yet certain whether it is an obligate intermediary, or formed only because of certain variations of the bacterial flora in the colon. It is regularly encountered after use of broad spectrum antibiotics.[21b, c] All three of the urobilinogens are colorless and exhibit the same intense Ehrlich reaction. In

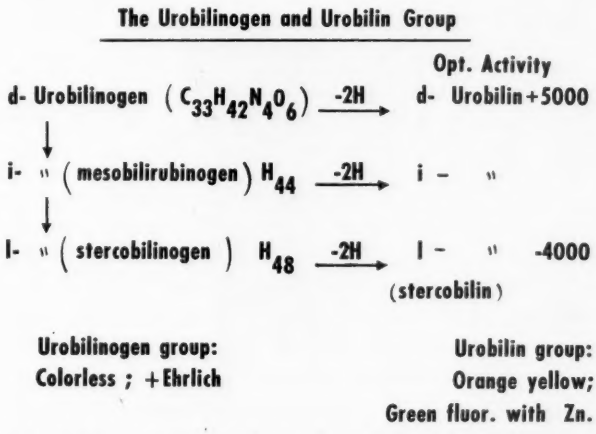

FIG. 3. Interrelations and characteristics of members of the urobilinogen and urobilin group. Although designated conveniently as d-, i-, and l-forms, it is recognized that the three members are not isomers.

addition to their differing optical activity, the three urobilins behave differently toward ferric chloride oxidation (figure 4) employed in accordance with earlier methods.[22, 23] The l-form, stercobilin, is stable, its original color and absorption being unchanged. The d-form, as seen at the right in figure 4, is converted mainly to the blue-green or aqua colored glaukobilin with maximal absorption at 650 mμ. The i-form is converted to a mixture of glaukobilin, mesobiliviolin and mesobilirhodin, with a composite blue or violet color and maximal absorption at 560–570 mμ. By comparison of optical activity and the results of ferric chloride oxidation, it is usually possible to gain a reasonably accurate insight as to the original proportions of the three types in any given sample of biologic material.

Extensive studies * with these methods, especially in hepatic and he-

* To be described in detail elsewhere.

molytic states, have failed to offer any support for a dichotomous concept of origin of the urobilins which has been championed in recent years by Baumgärtel and others in Germany.[24-27] According to this concept, i-urobilin is formed in the liver and is found in the urine only in the presence of liver injury, while the l-type is thought to be formed only by bacterial reduction in the colon, normally present in the urine and increased in hemolytic states. For reasons not clear, d-urobilin has been wholly disregarded by the Baumgärtel school, yet our studies with Lowry [21c] have established that it is easily reduced to the i-form either by normal fecal bacteria or by simple chemical hydrogenation. These studies show clearly that all three of the urobilins owe their formation to bacterial activity in the

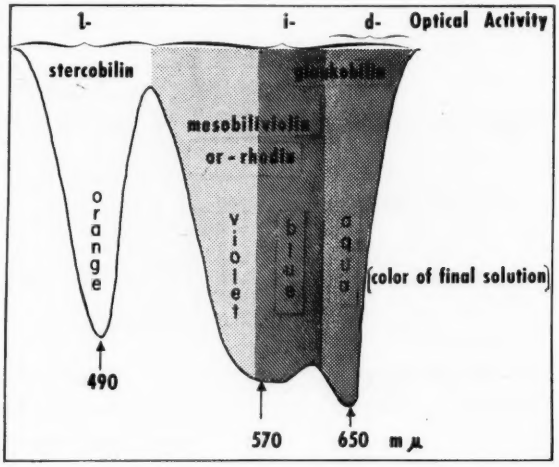

FIG. 4. A composite spectrogram of the derivatives of $FeCl_3$ oxidation of the three urobilins, in 1.5 N HCl. The aqua color is that of glaukobilin, the blue color that of glaukobilin with a smaller proportion of mesobiliviolin or mesobilirhodin, and the violet color that of a large proportion of the last two compounds in varying proportion. The solution derived from stercobilin is often a pinkish orange or yellow.

colon or, rarely, in the infected biliary or urinary tracts. In certain normal individuals i-urobilin has been observed in the feces and urine even in preponderance, although the l-type, stercobilin, is the usual representative normally. Studies with Lowry and others [21e] have shown that after the use of broad-spectrum antibiotics the feces, if examined serially over a long period, are found to contain successively a preponderance of d-urobilinogen, later more of i-, and finally more of l-. It is also believed to be highly significant that we have observed the formation of d- plus i-, from bilirubin, in broth cultures of fecal bacteria, even where the inocula were from normal feces containing a preponderance of the l-form. This is interpreted simply as a lack of optimal growth and metabolic conditions for the full reduction under the artificial circumstances of the experiment.

All of our results thus support the view that the variable composition of the urobilin group in feces and urine, both in health and in disease, is simply an expression of alterations in bacterial activity and absorption from different areas in the colon at any given time.

There are unanswered questions of practical significance as to the fate of bilirubin and urobilinogen in the intestinal tract. A number of years ago we administered crystalline bilirubin via duodenal tube to two patients with complete common duct obstruction.[28] The amount of urobilinogen which appeared in the feces was surprisingly small—only about 10%. There was no evidence of reabsorption of bilirubin, at least insofar as any elevation of icterus index was concerned. Subsequently it has been suggested that this very small recovery was due to a principal conversion of bilirubin or immediate derivatives to dipyrrylmethenes such as mesobilifuscin, henceforth referred to as MBF.[29] For this reason Dr. Gilbertsen in our group has recently repeated this type of study, using crystalline N^{15} bilirubin as previously isolated with Lowry.[30] The results will be described in detail elsewhere, and it will suffice to note at present that while the increase in urobilinogen after the bilirubin was again relatively small, that of the MBF was insignificant or entirely lacking. More important was the fact that the N^{15} tagging of the crystalline urobilin which was isolated was usually greater than that of the MBF, indicating that less of the latter compound had been formed. The basis for the great discrepancy between the fed bilirubin and the amount of urobilin appearing in the feces is still unknown, but it is clear that it cannot be explained by the formation of MBF. In view of Friedrich v. Müller's classic observation that bile feeding in a case of complete biliary obstruction was shortly followed by plentiful excretion of urobilin in feces and urine,[31] and having in mind the recent evidence that the bile bilirubin is conjugated with glucuronic acid,[32, 33, 34] we have recently repeated the earlier experiments using a crude concentrate of bilirubin glucuronide prepared from human bile according to a method devised in this laboratory by Dr. Malcolm Campbell. This will be described in a separate communication. As a rule a much more significant increase of urobilinogen has then been observed in the corresponding, carmine marked feces. This suggests that the reduction of the conjugated (polar) bilirubin by the colonic bacteria is much more efficient than that of free (non polar) bilirubin. In support of this concept recent experiments have shown that broth cultures of human fecal flora usually reduce the prompt direct-reacting bilirubin (glucuronide) of bile much more efficiently than does crystalline bilirubin.

This may have bearing on one of the most intriguing problems in the field of hemoglobin metabolism, i.e., the discrepancy between red cell life span and fecal urobilinogen in relation to the total circulating hemoglobin. This discrepancy is variable but at times quite marked. An outspoken example has recently been studied in some detail with Dr. Gilbertsen. This

occurred in a woman of 36 having a mild chronic refractory anemia with a total circulating hemoglobin of 380 gm. While the anticipated fecal urobilinogen for a normal 120-day red blood cell life span in relation to this amount of hemoglobin would be 133 mg.,[1] the observed amount over a considerable period of time was but 30 mg. If this accurately represented total hemoglobin catabolism, it would actually correspond to a life span of 469 days, which is scarcely credible, especially in the face of a normal Cr^{51} red cell life span. The t ½ was 27.5 days. It has been suggested that discrepancies of this type are due to a diversion of bilirubinoid compounds to dipyrrylmethenes or MBF,[29, 35] but the amount in the case just referred to was but 6 mg./d, under the normal range (7 to 20 mg./d.). This is inconsequential in explaining the discrepancy, which has also been noted in other cases, without significant increase of MBF. What other explanations may be considered?

1. It appears unlikely that failure of conjugation of bilirubin with glucuronic acid is responsible for the discrepancy. In the above case the bile bilirubin (duodenal drainage) was studied and found to be almost entirely polar in behavior (prompt direct l' diazo reaction).

2. Thus far, at least, there is no evidence of a compensatory "throttling" [28] of blood destruction in such cases—in other words, a lengthening of the red cell life span—or any evidence of conservation and reutilization of pigment ("Einsparung"). Siegel and Lowry * in our group, and London * in New York, have failed to find tagging of hemoglobin in (post hemorrhagic) anemic rats after giving N^{15} stercobilin.

3. There is a possibility of an abnormal reabsorption and destruction of bilirubin derivatives without utilization. No direct evidence of this has been adduced, but some recent observations point in this direction. An interesting experiment was carried out with Dr. Gilbertsen in the above case of refractory anemia. The data will be given in detail elsewhere, but the significant result may be stated as follows: As already noted, this patient's fecal urobilinogen was consistently low. A large amount of bilirubin was given intravenously in divided doses. It was anticipated that the fecal urobilinogen would increase proportionately, but surprisingly enough this did not occur, and in fact none of the administered bilirubin was accounted for. As yet no information is available as to the fate of bilirubin similarly administered in normal individuals. There is an earlier observation of possible significance to this question, i.e., that Felix and Moebus [36] showed years ago that urobilinogen is destroyed in vitro by liver homogenate.

Studies with Lowry and Gilbertsen have thrown considerable light on the question of origin of the fecal dipyrrylmethenes. Again, the most decisive results were obtained by means of the N^{15} labeling as first used by London and co-workers.[18, 37] In these studies, to be described in detail elsewhere, the initial N^{15} labeling of stercobilin and MBF was nearly simultane-

* Unpublished observations.

ous and similar in degree, but at the end of the red blood cell life span at 120 days, when the stercobilin N^{15} had risen again to very significant proportions, the MBF N^{15} was but slightly increased, indicating that little of it was derived from destroyed hemoglobin.

In the continuing study with Dr. Gilbertsen, observations in certain cases of anemia have supported the view that MBF is anabolic, at least to an important extent. As already noted, the normal range of fecal MBF is approximately 7 to 20 mg./d. In the refractory or hyporegenerative anemias the amounts are small, even though the fecal urobilinogen may be well within the normal range or actually increased in relation to the amount of circulating hemoglobin. Thus the urobilinogen-mesobilifuscin or U–MBF ratio is high. In hemolytic anemia, on the contrary, the amount of fecal MBF is quite large, so that the ratio is normal or reduced. It may be assumed that much of this MBF is of anabolic origin—in other words, excessive pigment unused in porphyrin biosynthesis on the pathway to heme. The finding that the fecal MBF is more of anabolic than of catabolic significance is in harmony with the idea of a pigment "complex" or pool, as advanced by Whipple in 1922;[38] but it now becomes evident that, at least under ordinary circumstances, this "complex" relates in relatively more important fashion to dipyrrylmethene compounds, while, in general, the tetrapyrrylmethene bilirubinoids are mainly catabolic in origin. Preliminary observations of mesobilifuscin excretion in untreated pernicious anemia, in which a much larger proportion of the excreted bilirubinoids are of anabolic origin (vide infra), indicate that an even greater proportion of the MBF is anabolic in character. In other words, the U–MBF ratio is relatively low.

The mechanism by which MBF is provided from anabolic sources is unknown. It is possible that bilirubinoid pigment, unused in heme synthesis, as discussed below, is converted to MBF, but, as noted in the foregoing, the studies with bilirubin administered parenterally or orally do not support this thesis. Shemin[2e] very reasonably postulates a primary formation of differing tripyrrylmethenes (figure 5) in porphyrin biosynthesis, from porphobilinogen. This, in effect, was suggested by Turner[39a] a number of years ago, and recently by Bogorad and Granick.[39b] As noted in figure 5, these yield dipyrrylmethenes which couple to produce differing porphyrin isomers. It is quite conceivable that a supply of excess dipyrrylmethene might be provided in this fashion. Siedel's analyses[40,41] of bilifuscin and mesobilifuscin have shown that they are dipyrrylmethenes, often polymerizing to give chains of variable length and of differing solubility characteristics. Use of the term "dipyrrylmethene" in relation to the fuscin compounds in the present paper is based entirely on Siedel's analyses. These have also indicated that the substituent groups are vinyl and propionic, or ethyl and propionic, respectively, corresponding to bilirubin and all of its meso-derivatives.[40] Since the dipyrrylmethenes to be anticipated in

Shemin's plan (figure 5) would have acetic and propionic substituents, an appropriate bioconversion, at least of acetic to vinyl or ethyl groups, would be required.

London [18] made the unusually stimulating observation that there is an early peak of N^{15} in the fecal stercobilin of normal individuals after the administration of N^{15} glycine. It is obvious that if stercobilin, as the chief excretory product of destroyed heme, was derived solely from destruction of mature circulating red blood cells, labeling would not be anticipated until about 100 days after the administration of the glycine. The finding of an early peak, in addition to the later, anticipated peak at the end of the red cell life span, has not yet been adequately explained. Several possibilities have been suggested: (1) That it is derived from hemoglobin built up in the bone marrow and broken down without ever gaining access to the circulation.[15, 42] As far as is known, hemoglobin is manufactured only in immature

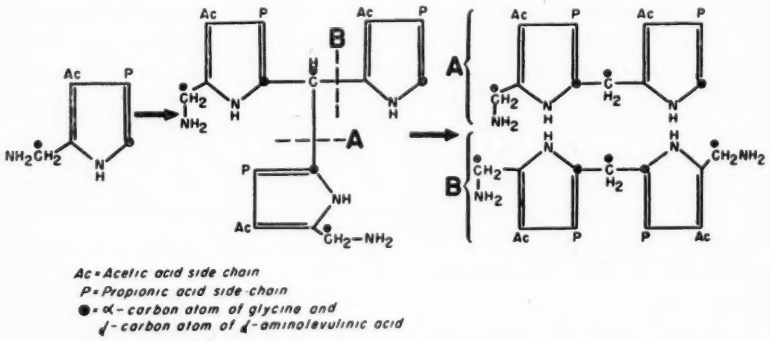

FIG. 5. The biosynthesis of porphyrin from porphobilinogen via a hypothetic tripyrrylmethene, and the dipyrrylmethene derivatives A and B.[2c] (Courtesy of D. Shemin and coworkers, J. Biol. Chem. **215**: 613, 1955. Reproduced by permission of the publishers.)

erythrocytes. This would imply that some cells are destroyed in situ and do not enter the circulating blood. (2) That it is derived from a pigment pool or complex, as suggested by Whipple (vide supra). This concept would simply require that a certain amount of tetrapyrrylmethene pigment, either porphyrin ring or bilirubinoid chain, is manufactured in excess of that used in the actual construction of hemoglobin, and that this moiety is then quickly represented by bilirubin in the bile and subsequently by stercobilin in the feces. As discussed in earlier papers,[1, 28] there is evidence that this mechanism is operative in pernicious anemia, in which a much larger proportion of the fecal stercobilin is derived from sources other than mature circulating red blood cells,[37] and in which, because of the striking megaloblastic arrest in the bone marrow, it is scarcely surprising to find a faulty utilization of pigment not actually brought to the final stage of hemoglobin, nor sent forth in circulating red cells. London and West's

study [37] also showed a random destruction of red cells in untreated pernicious anemia, resulting in a moderately decreased red cell life span, but it was calculated that about 60% of the stercobilin was from sources other than destroyed circulating erythrocytes. (3) There is also the possibility that, even under normal circumstances, young erythrocytes are fabricated in excess of the actual need, and that some of these are at once destroyed.[15] This would be quite in line with the general lavishness of nature and the frequency with which it compensates in excess. Some evidence in this direction has recently been discussed.[1] Dr. Berendes in this laboratory has subsequently made some interesting observations on the relative numbers of reticulocytes in the splenic pulp. In this study, to be described in more detail elsewhere, it was found that the reticulocyte percentage in the spleen is significantly higher than in the circulating red cells. This, of course, does not prove that the reticulocytes are being destroyed in the spleen. Crosby [43] believes that they pause there for a few days to mature, in this process becoming smaller and less sticky because of loss of some of the lipid in the red cell membrane. At the same time the possibility must be admitted that at least some of them are unable to escape, and undergo destruction. It appears unlikely, however, that this would account for the appearance of N^{15} in the fecal stercobilin earlier than 36 to 48 hours after the administration of N^{15} glycine. Yet in one of our N^{15} glycine studies * in a case of hemolytic jaundice, it was observed that the stercobilin was significantly tagged as early as 12 hours after the glycine administration had been started. This, of course, points much more strongly toward the second of the above concepts, that of an unused moiety of pigment. It is quite possible that the early N^{15} stercobilin peak is a composite of the second and third mechanisms.

A few comments are desirable as to some practical aspects of urobilinogen determinations in clinical practice. It is clear, especially from studies with Sborov,[21b] that broad spectrum antibiotics will interfere in varying measure with the bacterial reduction of bilirubin to the urobilinogen group, and that values for the latter in such cases will be unduly low. Within a few days of discontinuance of the antibiotic the reduction in the colon is resumed, but for some time, often months, the urobilinogen is represented by the dextrorotatory type rather than by the normal levorotatory stercobilin or 1-form [21e] (vide infra).

Because of the variable failure of urobilinogen determinations to represent red cell destruction in quantitative fashion, some have advocated abandonment of the urobilinogen determination in the clinical study of blood destruction in favor of Cr^{51} red cell life span determinations. The latter are time-consuming and by no means generally available, even if they can be accepted as the court of last appeal, which is not fully established. The simple fecal Ehrlich determination for urobilinogen [44] on a random sample

* With Dr. Paul Lowry, unpublished.

may at once give decisive information as to a heightened rate of red cell destruction. Thus, if a patient presents with anemia and is found to have more than 500 Ehrlich units per 100 gm. of feces, the diagnosis of excessive hemolysis is at once assured, whereas if the value is less than 200 Ehrlich units, excessive hemolysis is much less likely. In the study of hemoglobin metabolism in the anemias in this laboratory, it has been customary for years to obtain a random sample at the outset; but if the result in Ehrlich units is indecisive or borderline, a four-day collection for fecal urobilinogen is then carried out. The per diem value is calculated in relation to the total circulating hemoglobin as the "apparent wastage," or W value.[1, 28] Normally this ranges from 0.4 to 0.8% daily. Calculation of this value considerably sharpens the sensitivity of the fecal urobilinogen determination. In the light of what has been said in the foregoing, it is fully recognized that a variable fraction of the fecal urobilinogen is derived from sources other than the destruction of mature circulating red cells, consequently the term "apparent wastage."

Concluding Remarks

I will close with some words of Fuller Albright, who was the John Phillips Medalist 10 years ago:

1. I have told you more about hemoglobin metabolism than I know.
2. I hope I have raised more questions than I have given answers.
3. In any case, as usual, a lot more work is necessary.

May I acknowledge again my great pleasure and privilege in giving the twenty-first John Phillips Memorial Lecture.

Summario in Interlingua

Es discutite, in summarios contrastante, certe aspectos anabolic e catabolic del metabolismo de heme. Es sublineate le character essentialmente anabolic del porphyrinas e etiam le signification de porphyrinogenos in le transito biosynthetic ab porphobilinogeno a heme. Le sequentias catabolic es representate principalmente per le bilirubinoides a catena aperte, durante que le membros del categoria de dipyrrylmetheno o de fuscina es plus importante ab le puncto de vista anabolic. Iste ultime facto deveniva evidente in studios de glycina a N^{15} in que le mesobilifuscina fecal monstrava un culmine de attingimento rapide sed pauc augmento al tempore del secunde culmine de N^{15} in le stercobilina, correspondente al destruction de matur erythrocytos circulante. In plus, le mesobilifuscina fecal in casos de anemia refractori o aplastic es disproportionatemente parve; le proportion de urobilinogeno a mesobilifuscina es alte; sed le tendentia contrari es a notar in le anemias hemolytic.

Studios additional del gruppos urobilinogenic corrobora le concepto del derivation enterogene de omne tres membros, i.e. le formas d-, i-, e l-. Es sublineate le facto que il non se tracta hic de isomeros. Le designationes supra-usate constitue simplemente un methodo practic pro identificar simile membros de un gruppo. Es discutite le datos concernente le genese bacterial del tres formas e le transition ad d- via i- a l-. Nulle supporto esseva trovate pro le conception que le forma i- (mesobilirubinogeno) es generate in le hepate e non per un activitate bacterial in le colon.

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THE CLINICAL ASPECTS OF CEREBRAL VASCULAR INSUFFICIENCY *

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Transient cerebral vascular disturbances are of common occurrence and have been observed by most clinicians. When such episodes result from widespread cerebral ischemia, they are ordinarily manifested by such familiar signs as syncope or grand mal seizures. However, when the cerebral vascular disturbance is more localized, transient focal signs and symptoms will appear. The specific clinical manifestations in these cases depend upon which particular cerebral region has been affected. Thus, a great variety of manifestations have been observed in different cases, including transient hemiplegia, hemianopsia, monoplegia, aphasia, paresthesia, localized convulsive phenomena, etc. It is well known that a given patient may display the same sign or symptom repeatedly, with complete recovery between each episode.

The Question of Cerebral Angiospasm

It is generally agreed that these "little strokes" are the result of localized cerebral ischemia. Because of their sudden onset and usually rapid disappearance, it has become customary to attribute these ischemic phenomena to cerebral vascular spasm. This mechanism appears to offer a simple and convenient explanation for transient episodes of localized cerebral ischemia which are not readily explicable on any other basis.

It is obvious, however, that the mechanism of cerebral angiospasm requires that the cerebral vessels be supplied with innervation and musculature adequate to cause effective contraction. Until recently it has been tacitly assumed that such apparatus was present. The investigations of Pickering,[1] however, have thrown considerable doubt on the validity of this assumption, since he was unable to demonstrate a vasomotor apparatus in the cerebral vessels. There is some evidence that the arterial system of the circle of Willis and the arteries proximal to this area contain vasomotor innervation, and it is fairly certain that the meningeal arteries are so supplied, but it remains highly doubtful that the arteries within the cerebral substance,

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particularly those beyond the circle of Willis, are endowed with a nerve supply. These considerations led Pickering to regard the mechanism of cerebral vasospasm as highly improbable.

The conclusion that the cerebral vessels cannot contract seems supported by the observations of Walker [2] who, in a series of over 800 cerebral angiograms, has never noted evidence of spasm of these vessels during the procedure. Conflicting opinions have been expressed by other observers [2b, 3] concerning the occurrence of cerebral vasospasm during cerebral angiography. In this connection, it should be pointed out that narrowing of cerebral vessels during angiography may be passive in character, occurring as a result of spasm of the proximal, injected carotid vessel, with consequent diminution of pressure in the cerebral vessels themselves.

The most complete study of the problem of cerebral angiospasm was that published by Forbes in 1933.[4] Forbes measured the contractility of pial vessels and found that stimulation of the cervical sympathetic nerves reduced the luminal diameter of the pial vessels by a mere 7%, while an artery of comparable size in the skin of the ear underwent a reduction of 56% in its internal diameter. Adrenalin applied locally constricted cerebral arteries only feebly. Indeed, close scrutiny of the results of these studies raises considerable doubt that the evidence for constriction of the pial vessels is statistically significant. Furthermore, Forbes's investigations were carried out mainly on cats, whose pial vessels differ from those in man in both innervation and musculature.

As an alternative to the mechanism of angiospasm, Pickering [1] advanced the theory that most "small strokes" are due to small cerebral thromboses or emboli. In support of this explanation he cited the frequent occurrence of auricular fibrillation in these patients. This condition could, of course, provide a source of emboli. However, many cases have been reported in which numerous transient strokes have been sustained in the absence of a cardiac arrhythmia or any other detectable source of embolization. In some instances, as many as nine such attacks have occurred involving the same cerebral area repeatedly. To explain the rapid restoration of normal cerebral function in many of these cases, he suggested several possible mechanisms: (1) the collateral vessels open and restore the circulation to all or part of the ischemic territory; (2) the hemorrhage or edema initially surrounding the ischemic brain tissue is gradually removed; (3) the obstructing clot is recanalized, and (4) if embolism has occurred, the embolus moves or is forced into a side branch. However, there are serious objections to most of these postulated mechanisms. Because it takes a considerable time for absorption of hemorrhage and edema and for recanalization of the clot, and because the clinical evidence of most of these transient attacks disappears rapidly, it is highly unlikely that these postulates can adequately explain all of the transient strokes. Further, it seems improbable that all emboli in a given patient can be expected to dislodge themselves and move on. It is also

difficult to believe that emboli would repeatedly strike only one particular area and make it more vulnerable than other areas. Pickering's suggestion —that rapid recovery might result from the opening of collaterals in the affected area—seems reasonable, but hardly explains those instances where a single area is repeatedly involved.

Because serious doubt concerning the existence of cerebral angiospasm had been raised, the authors [5] carried out a series of experiments on rhesus monkeys designed to provide further information about this problem. This animal was chosen because its cerebral vasculature more nearly resembles the human than does that of any other animal. The results of these experiments clearly indicate that the pial vessels do not change caliber under direct mechanical stimulation when hot or cold stimuli are applied or after local application of adrenalin. These vessels were seen to vary in caliber when significant changes in the systemic blood pressure were induced. It was observed that when the systemic pressure was lowered by bleeding or by the administration of a hypotensive drug, the pial arteries narrowed significantly. This was also observed to occur after the onset of hypotension subsequent to the parenteral administration of aminophylline, which is contrary to the general belief that this drug causes cerebral vasodilatation. On the other hand, when systemic blood pressure was again raised by the transfusion of blood, or by the intravenous injection of pressor drugs, the caliber of the pial arteries increased. Since these changes in arterial size always followed the changes in systemic blood pressure, it was concluded that they were purely passive in character and were not a vasomotor phenomenon.

The evidence obtained from these experiments thus provides strong support for the view that cerebral angiospasm does not occur. It is true that only the pial vessels were studied, but there is no reason to doubt that intracerebral arterioles function in a similar manner. It is possible also that the large arteries proximal to the circle of Willis may be capable of active contraction, but such a phenomenon would be expected to give rise to widespread cerebral ischemia, and not the localized signs with which we are chiefly concerned. Thus, from both anatomic and physiologic evidence, it seems fair to state that cerebral angiospasm is an improbable phenomenon and an unsatisfactory explanation for transient localized cerebral ischemic episodes.

Cerebral Vascular Insufficiency

Because of these considerations, and because of the objections to Pickering's alternative explanations, it became desirable to attempt a new approach to this problem. In 1953 the authors developed the concept of "cerebral vascular insufficiency," [6, 7] which appears to provide a more satisfactory explanation of "little strokes" than had previously been offered. Acute cerebral vascular insufficiency may be defined physiologically as a deficiency of the cerebral arterial blood flow resulting from an inadequate systemic arterial blood pressure or impairment of the cardiac output, usually in the

presence of narrowed cerebral arteries. Although the condition is often transient and reversible, if it is not promptly corrected permanent brain damage may result. Clinical symptoms will arise if the cerebral vascular deficit is severe enough to deprive the cerebral cells of adequate nutrition. The vascular insufficiency may involve the whole brain or it may be localized. When it is generalized, syncope, grand mal seizures, etc., may occur. When the vascular insufficiency is localized, such focal cerebral manifestations as hemiplegia, hemisensory disturbances, Jacksonian seizures, etc., will result. A reduction in systemic blood pressure may cause focal cerebral ischemia by decreasing blood flow through an already narrowed cerebral artery, especially when the fall in systemic pressure is so pronounced that the collateral

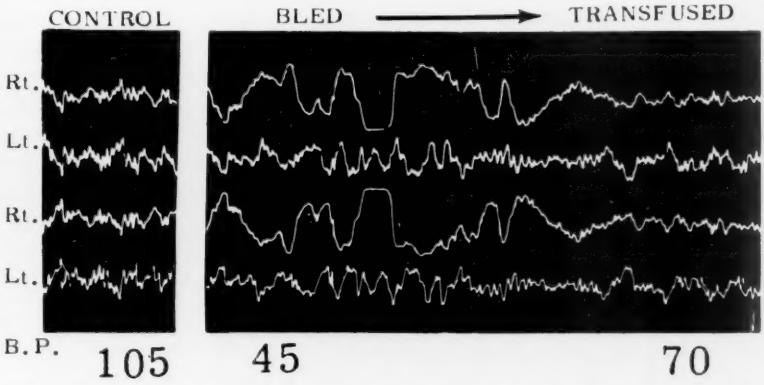

FIG. 1. Control electroencephalograms of a monkey which were recorded simultaneously after the right internal carotid and vertebral arteries had been narrowed to approximately one third their diameter with Goldblatt clamps. With a mean blood pressure of 105 mm. Hg, the electroencephalogram on both sides was normal. When the animal was bled and the blood pressure reduced to a mean of 45 mm. Hg, large slow waves developed on the right side. When the animal was transfused and the blood pressure reached 70 mm. Hg, the electroencephalogram again became completely normal.

circulation to the affected cerebral region becomes inadequate for the cellular metabolic requirements.

It will be observed that the concept of cerebral vascular insufficiency is closely analogous to the concept of coronary insufficiency as developed by Master and his associates.[8, 9] As in coronary insufficiency, correction of cerebral vascular insufficiency depends upon prompt restoration of the systemic blood pressure or cardiac output, but if either condition is allowed to persist, death of the ischemic tissue will occur. Thus, with cerebral vascular insufficiency, prompt and vigorous measures to correct the underlying extracerebral precipitating factor may prevent permanent neurologic disorders.

The mechanism of cerebral vascular insufficiency was demonstrated in our experiments on the monkey.[6] It was shown that transient electroencephalographic abnormalities occurred when systemic hypotension was

produced in animals whose carotid and vertebral arteries were narrowed on one side by occlusive clamps (figure 1). It was further demonstrated that the electroencephalographic changes could be reversed when the monkey's blood pressure was restored to normal by either transfusions of blood or the administration of vasopressor agents. In several experiments, while the animal was still anemic because of acute loss of blood, vasopressor agents were given and the electroencephalographic changes disappeared. This indicated that the ischemic electroencephalographic changes were due to the drop in blood pressure itself, rather than to the anemia. Thompson [10] completely occluded the middle cerebral artery in monkeys and then produced hypotension in some of them. In the animals that remained hypotensive for a considerable time, electroencephalographic changes and clinical signs of severe cerebral damage resulted. However, in the group of monkeys that remained normotensive following the arterial occlusion, no electroencephalographic or other neurologic disturbance occurred. Many authors, among them Egas Moniz [11] and Denny-Brown,[12] have postulated that cerebral ischemia occurs in patients with cerebral thrombosis who develop a drop in systemic blood pressure. However, our studies demonstrate that, with a narrowed vessel but without actual occlusion, transient cerebral disorders can result from hypotensive episodes.

Symptoms and Signs of Cerebral Vascular Insufficiency

Our experimental studies suggest that either focal or generalized neurologic changes can occur during a hypotensive state in the patient with narrowed cerebral arteries. When the blood pressure is normal, the capillary pressure distal to the narrowed or obstructed vessel is sufficient to supply the demands of cellular metabolism. However, as the cells of the nervous system are particularly vulnerable to nutritional deprivation, their blood supply cannot long be withheld without the occurrence of severe or irreversible damage. If the collateral blood supply is sufficient to care for the area supplied by the narrowed or obstructed vessel, the nutrition of this area will be satisfactory and ischemic signs and symptoms will not occur. However, if the blood pressure is significantly lowered, the collateral supply will fail and the trickle of blood which is crossing the narrowed vessel will also further diminish. The area will then become ischemic, and focal neurologic signs such as hemiplegia, hemianesthesia, confusion, syncope, coma, Jacksonian convulsive seizures, focal paralysis, aphasia and astereognosis can occur. If there is more generalized ischemia, syncope, coma or grand mal seizures will result.

As will be shown later, the clinical picture of cerebral vascular insufficiency may be precipitated not only by systemic hypotension per se, but also by other disturbances in circulatory dynamics, which may result in a reduced intracerebral blood flow. Cerebral disorders of a focal or generalized type are often seen—for example, in the presence of diminished cardiac output,

or with a diversion of systemic blood to the extremities or abdomen, or when a marked reduction in circulating blood volume occurs. The common denominator in all these conditions is a diminution in intracerebral blood pressure. It is also important to note that all these conditions are potentially correctable if treated promptly and adequately. Since cerebral cells are particularly sensitive to ischemia, such early treatment of the responsible systemic factors is of the utmost importance to prevent the occurrence of irreversible brain damage.

The symptoms and signs of cerebral vascular insufficiency are similar to those of an acute cerebral thrombosis. However, the symptoms of the precipitating cause of the cerebral vascular insufficiency may often mask or confuse this clinical picture. For example, if the precipitating cause is a hypotensive state, the patient will exhibit pallor, sweating, a cold clammy skin, dyspnea, etc. If a coronary artery occlusion or cardiac arrhythmia has induced the cerebral vascular insufficiency, the patient might also have chest pain, palpitation and breathlessness. Very often, the symptoms of a hemorrhage, arrhythmias or a myocardial infarction may be silent and will not be detected without the aid of laboratory tests. The clinician should attempt to take a careful history as regards to the timing of the symptoms in all cerebral strokes because these symptoms often occur prior to the onset of the cerebral symptoms. Of course, coma may be the first sign of cerebral vascular insufficiency, in which case it is most difficult to elicit a satisfactory history except from witnesses.

Clinical Conditions in Which Cerebral Vascular Insufficiency May Occur

I. *Hemorrhagic Shock:* It has been known for centuries that the brain may be injured as a result of remote hemorrhage.[13, 14, 15] It is now realized that the cerebral damage is due to the attendant systemic hypotension and shock, rather than to the anemia.[6] Many instances have been reported which fulfill the criteria for cerebral vascular insufficiency during or immediately following an episode of bleeding. We have seen a number of patients who developed hemiplegia during severe gastric or intestinal hemorrhage. When the associated hypotension was corrected by blood transfusion or vasopressor drugs, the hemiplegia disappeared. Bedford [16] stated that in a group of elderly people who had sustained an acute hemorrhage the incidence of dementia was about one in 15. It is not unusual for the patient to present primarily the symptoms and signs of a cerebral accident. In such cases the cause of the neurologic disorder may be overlooked. In every instance of a cerebral vascular accident, therefore, the clinician should search for evidence of remote bleeding from the gastrointestinal tract or elsewhere, especially if hypotension is present.

II. *Coronary Shock:* Cole and Sugarman,[17] Bean and Reed [18] and Hicks and Warren [19] have shown that the presenting and sometimes the only symp-

tom of a coronary occlusion may be a cerebral disturbance. We have also seen a number of patients who were admitted to the hospital with the diagnosis of massive cerebral thrombosis. These patients were in shock and remained in this state until the time of their death. To our surprise, at autopsy the cerebral arteries were found to be narrowed but patent. The cause of the hypotensive state in these cases was an unsuspected coronary thrombosis.[6] We believe that when a patient is seen in coma, or presents other neurologic signs suggesting cerebral ischemia, consideration should always be given to the possibility that a coronary occlusion has occurred.

III. *Anaphylactic Shock:* We have seen patients who developed hemiplegias, etc., due to anaphylactic shock. When they were adequately treated with vasopressor drugs no residual signs or symptoms remained.

IV. *Insulin Shock:* We have reviewed the record of a patient who developed severe hypotension due to an overdose of insulin. While this patient was in a hypotensive state for a two-hour period she presented the signs and symptoms of a hemiplegia. When the hypotensive state was corrected the hemiplegia disappeared.

V. *Traumatic Shock:* It has long been noted in the literature that patients may develop neurologic disorders simulating those due to a cerebral thrombosis following severe trauma elsewhere in the body. However, in many of these cases that were autopsied no cerebral thrombosis could be found. It is our belief that in such cases the cerebral signs were manifestations of cerebral vascular insufficiency secondary to traumatic shock.

VI. *Antihypertensive Drugs:* Sampson,[20] Grimson et al.[21] and others have described patients who developed severe neurologic disorders due to overenthusiastic treatment with vasodepressor drugs such as Methonium. These authors suggest that patients who have known cerebral artery disease and require treatment for essential hypertension should be treated with great caution lest they sustain too sharp a drop in systemic blood pressure. It must be realized that such patients may require an elevated systemic blood pressure to maintain an adequate collateral cerebral circulation.

VII. *Postsympathectomy:* Rabwin [22] has described two patients upon whom he performed successful sympathectomies for treatment of essential hypertension. Hemiplegia subsequently occurred in both.

VIII. *Hypersensitive Carotid Sinus:* Askey [23] has reported hemiplegia in patients with hypersensitive carotid sinus following massage of the carotid sinus. We have reported [7] on a patient with a hypersensitive carotid sinus who developed cardiac asystole and a drop in blood pressure. At autopsy it was found that the patient had arteriosclerotic narrowed cerebral arteries and patchy areas of cerebral infarction. Clinically, the patient had frequent episodes of various transient neurologic disorders.

IX. *Postural Hypotension:* We have recorded electroencephalograms on a patient who, upon assuming the erect position, sustained a severe drop in systemic blood pressure (figure 2). When he stood erect the systolic blood

pressure fell from 102 mm. Hg to 50 mm. Hg. At this time he complained of dizziness and a feeling of great weakness and numbness of the extremities. When the blood pressure returned to normal within two minutes, the signs and symptoms disappeared and the electroencephalogram returned to normal. Meyer et al.[24] have recently confirmed this and suggested that a "tilt table electroencephalogram test" be performed to detect cerebral artery insufficiency. Chew, Allen and Barker [25] found neurologic signs in 23% of their cases of orthostatic hypotension. Baker [26] has shown that patchy sclerosis of the brain and spinal cord may be the result of intermittently disturbed

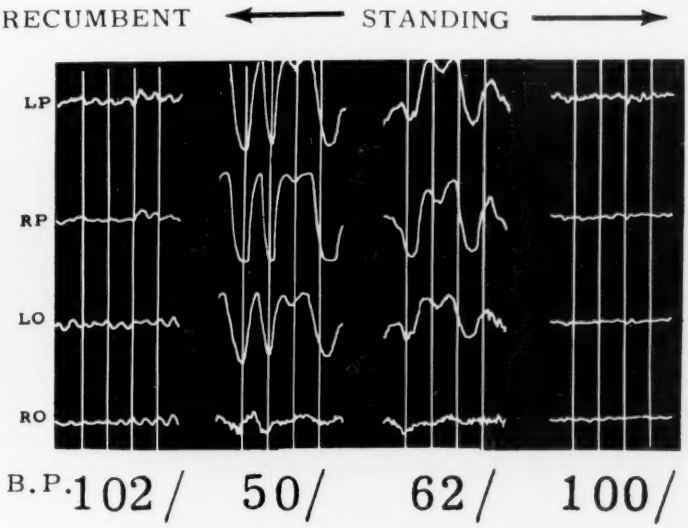

FIG. 2. Electroencephalograms recorded in a man aged 86 who complained of dizziness, feeling of weakness and numbness of the extremities when standing erect. When the systolic blood pressure was 102 mm. Hg, the electroencephalograms were completely normal. However, when he suddenly stood erect and the systolic pressure dropped to 50 mm. Hg, large slow waves developed in some leads. The systolic blood pressure rose to 100 mm. Hg within two minutes while the patient was standing, and the electroencephalograms returned to normal.

circulation of these organs incident to postural changes in the systemic blood pressure.

X. *Hypotensive Episodes of Reflex Origin:* Engel et al.[27] recorded electroencephalograms on patients who developed syncope and a marked drop in blood pressure due to distention of a viscus such as the stomach or vagina, or during venipuncture. These patients showed electroencephalographic changes of cerebral ischemia which were transient. When the blood pressure returned to normal the electroencephalograms also became normal again. Thus, it is entirely possible that some clinically unrecognized transient cere-

bral episodes might be due to hypotension resulting from vasodepressor reflexes.

XI. *Cardiac Arrhythmias:* We have observed a patient who developed neurologic disorders due to paroxysmal ventricular tachycardia.[7] Barnes in 1926 [28] reported a large series of patients who developed neurologic disorders as a result of rapid arrhythmias. We have also seen patients with severe cerebral arteriosclerosis who developed neurologic disorders in association with frequent premature ventricular systoles. It has long been recognized that transient focal and generalized neurologic disorders result from bradycardia in heart block and from changing arrhythmias, as in the Adams-Stokes syndrome.[29] In most cardiac arrhythmias there is sufficient decrease in cardiac output to cause cerebral vascular insufficiency.[37]

XII. *Surgical Procedures:* It is well known that patients can develop hemiplegia or other neurologic disorders as the result of a drop in blood pressure or the occurrence of cardiac arrhythmias during surgical procedures.[30]

XIII. *Anesthetics:* Not rarely, as the result of hypotension due to oversedation, or a tachycardia which occurs as the result of a chemical anesthetic, severe neurologic disorders may develop. These may be temporary or permanent. In a recent study van Dam [31] recognizes this sequence of events.

XIV. *Congestive Heart Failure:* It has been pointed out [32] that neurologic disorders can result from congestive heart failure. It is entirely possible that, due to hypotension or the low cardiac output in left heart failure, cerebral vascular insufficiency can occur.

XV. *Pulmonary Hypertension:* We have studied the autopsy material of patients with marked pulmonary hypertension due to fibrotic tuberculosis who had developed recurrent transient hemiplegias. The cerebral vessels were not thrombosed but were narrowed by an arteriosclerotic process. Despite the absence of thrombosis, a patchy cerebral infarction was found. It is a well recognized clinical fact that patients with pulmonary hypertension often develop syncope. The probable cause for most of these neurologic signs would seem to be a transient reduction in cardiac output or compression of the coronary arteries.[36]

XVI. *Thermal Vasodilatation:* Goldblatt [33] has observed patients who developed transient cerebral disorders as a result of vasodilatation due to steam baths. These cerebral episodes were of a transient nature and probably were due to a pooling of blood in the cutaneous circulation resulting in cerebral ischemia.

XVII. *Valsalva Maneuver:* It is a common occurrence that patients during severe coughing spells or while straining at stool develop transient cerebral disorders. This may well be due to a drop in systemic blood pressure or cardiac output associated with these actions.[34] Syncope or focal cerebral signs may occur, depending upon the extent of the cerebral vascular insufficiency.

XVIII. *Gravitational States:* It has been reported that in patients who have been inactive during prolonged automobile travel, the blood will pool in the lower extremities. Soffer [35] described a patient who, due to a long automobile ride in the upright position, developed cerebral ischemia. The patient had grand mal convulsions. It is postulated that in the gravitational states of rapid acceleration, as in airplanes, where pooling of blood occurs, if the patient has a narrowed cerebral artery due to congenital defect or arteriosclerosis, cerebral vascular insufficiency will be encountered.

XIX. *Angiography:* We have observed several patients who developed hypotension following the injection of Diodrast for angiography. Transient cerebral signs or permanent cerebral damage occurred, probably due to the concomitant hypotension during the procedure.

XX. *Hypothermia:* It is recognized that where refrigeration technics have to be used in surgery, due to the low cardiac output caused by the bradycardia, permanent cerebral damage may result.

XXI. *Sleep:* The authors have attended patients who developed focal cerebral disorders such as weakness and numbness of the limbs whenever they fell asleep in the upright position. Jimenez-Diaz [38] has noted that hypotension can occur in sleep particularly if the patient has been heavily sedated.

XXII. *Pulmonary Embolism:* Israel [39] has recently described the occurrence of cerebral vascular insufficiency which was induced by pulmonary emboli.

To this wide variety of clinical conditions in which cerebral vascular insufficiency may occur, others will probably be added as experience is accumulated. The specific neurologic manifestations of this syndrome are also extremely varied and depend, of course, upon which cerebral vessel or vessels are most compromised. A complete discussion of the many signs and symptoms which may arise as a result of failure of the collateral circulation in the territory supplied by these arteries is beyond the scope of this paper. It may be said, in general, that the neurologic manifestations of cerebral vascular insufficiency are not different from those of cerebral thrombosis except that their onset may be more abrupt and that they are more often reversible. It is certain that the transiency of many of these cerebral episodes is the result of spontaneous homeostatic mechanisms. However, the clinician should not depend upon the efficacy of these mechanisms, which frequently fail. He should therefore institute measures to correct the precipitating hemodynamic abnormality as rapidly as possible. In some instances, where such treatment is ineffective, or administered too late, the physician will also have to treat the resulting cerebral infarction, with its serious consequences.

Treatment of Cerebral Vascular Insufficiency

(1) *Extracerebral Factors:* (a) Prevention: In the patient with known cerebral arterial disease, every effort must be made to avoid an excessive drop in systemic blood pressure or a reduction in cardiac output. Anti-

hypertensive and anesthetic drugs must be used with great care in the patient with cerebral artery narrowing. Steam baths, vasodepressor procedures, stimulation of the carotid sinus, straining at stool, violent coughing and sleeping in an erect position should be avoided in such a patient.

(b) When the cause of cerebral vascular insufficiency is determined, appropriate therapy must be instituted. When it is precipitated by blood loss the blood must be promptly replaced. If blood is unavailable, plasma expanders or vasoconstrictors such as noradrenalin should be used without delay. If the cerebral disorder is precipitated by a hypotensive state resulting from coronary thrombosis, excessive sedation or anesthesia, insulin shock, anaphylactic shock, angiography or antihypertensive drugs, vasoconstrictor agents such as noradrenalin must be used promptly. Cardiac arrhythmias must be prevented, especially in the patient with cerebral artery narrowing. If they occur despite prophylactic treatment, antiarrhythmic agents must be used. When hypotension results from a tachycardia, vasoconstrictor drugs should be used with the antiarrhythmic agent until the arrhythmia has been abolished. Postural hypotension should be prevented by wrapping the limbs, avoiding sudden changes in posture or the use of vasopressor substances.

(2) *Treatment of the Neurologic Disorder:* If the cerebral manifestations of an episode of cerebral vascular insufficiency cannot be completely abolished by treatment, the remaining neurologic disorder must then be treated. The exact measures to be employed will be dictated by such considerations as the patient's general condition and the extent and location of his neurologic disturbance. Generally speaking, such routine treatment as careful nursing, prophylaxis against intercurrent infections, early ambulation and physical rehabilitative therapy will be indicated.

The indications for anticoagulant therapy to prevent actual thrombosis of an already sclerotic cerebral artery are not yet clear. This problem needs further study. Whether stellate block would be useful in patients with cerebral vascular insufficiency is also open to question. de Takats [36] stated that stellate block may have a beneficial effect in cerebral vascular insufficiency because it may improve the collateral circulation by reducing the resistance of the extracranial arteries. This requires experimental confirmation. In our experience, however, this procedure is unreliable and cannot be routinely recommended.

Summary and Conclusions

1. The concept that cerebral angiospasm can cause transient cerebral disorders has been considered. Experimental evidence strongly suggests that spasm does not occur in the human cerebral vessels, and thus cannot be responsible for cerebral disturbances.

2. The concept of cerebral vascular insufficiency has been offered as an explanation of a variety of hitherto vaguely understood clinical cerebral

phenomena. As a result of anatomic and physiologic considerations and experimental investigations, it is believed that in the presence of systemic hypotension or reduced cardiac output, the collateral circulation of the brain fails to supply the requirements of the cerebral tissue whose arterial flow has been compromised. If the systemic pressure is raised promptly to normal levels, the collateral circulation again becomes adequate and the cerebral signs and symptoms quickly disappear. If the hypotensive state is allowed to persist, permanent cerebral damage will result. It is important for the clinician to prevent a drop in cardiac output or systemic blood pressure in the patient with narrowed cerebral arteries. If hypotension or a drop in cardiac output does occur, it is imperative to institute prompt measures to restore the blood pressure by blood transfusion or by the administration of vasopressor agents.

3. Twenty-two clinical conditions are discussed in which the phenomena of cerebral vascular insufficiency have been observed. In each condition, systemic hypotension, a drop in cardiac output, or a diversion of blood from the brain has occurred in the presence of cerebral vascular narrowing.

Acknowledgments

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Summario in Interlingua

Acute insufficientia cerebro-vascular pote esser definite physiologicamente como un deficientia del fluxo de sanguine cerebro-arterial como resultato de inadequate pression de sanguine arterial systemic o de defectos del rendimento cardiac, usualmente in le presentia de restringite arterias cerebral.

Ben que le condition es frequentemente transitori e reversibile, permanente insultos cerebral pote resultar si illo non es corrigite promptemente. Un reduction del pression de sanguine systemic es capace a causar focal o generalisate ischemia cerebral per reducer le fluxo sanguinee in un jam restringite arteria cerebral, specialmente si le reduction del pression systemic es si pronunciate que le circulation collateral non pote mantener se.

Experimentos in simias e observationes in humanos ha demonstrate clarmente que le pression de sanguine systemic e le rendimento cardiac debe esser sustenite in patientes con restringite arterias cerebral pro evitar un resultante serie insulto cerebral.

Es discutite 23 conditiones clinic in que le phenomenos de insufficientia cerebro-vascular ha essite observate: in statos de choc—hemorrhagic, coronari, anaphylactic, post insulina, traumatic, etc.; como resultato del uso excessive de drogas antihypertensive; in statos postsympathectomic; e con hypersensibilitate del sinus carotic, hypotension postural, episodios hypotensive de origine reflexe, arrhythmias cardiac, interventiones chirurgic, anestheticos, congestive insufficientia cardiac, hypertension pulmonar, vasodilatation thermic, manovra de Valsalva, effectos gravitational, angiographia, hypothermia, somnio in position erecte, labyrinthitis, e embolismo pulmonar.

In omne iste conditiones, hypotension systemic, reduction del rendimento car-

diac, o diversion de sanguine ab le cerebro ha occurrite in le presentia de restriction cerebro-vascular.

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GASTRIC SECRETION AS INFLUENCED BY RAUWOLFIA ALKALOIDS *

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Rauwolfia and its various alkaloids have been recommended in the treatment of gastrointestinal syndromes because of their tranquilizing effects. But their stimulating effects on gastric secretion have made it difficult to determine the indications for their use.

I. Studies with Intravenous Reserpine: The methods used in these studies have been previously reported.[1, 2] Briefly, all subjects were studied after an overnight fast. A Levin tube was placed in the stomach and in every in-

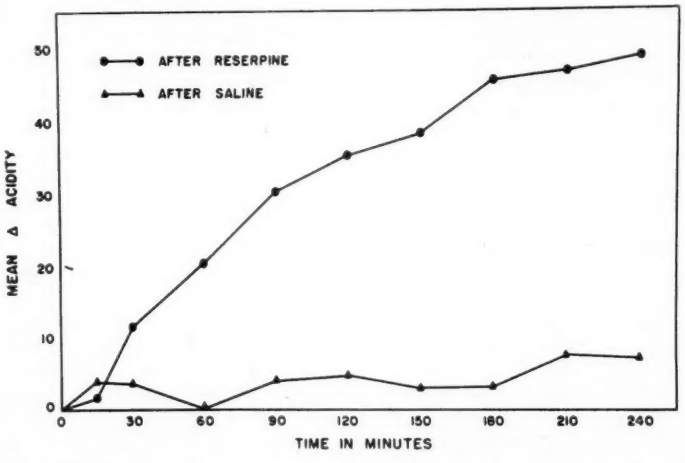

Fig. 1. Mean change in free hydrochloric acid (△ acidity) plotted for each collection period for both reserpine and control groups. (Reproduced from a previous publication [1] by permission of *Gastroenterology.*)

stance baseline determinations of gastric acid were made over a 30- to 90-minute period prior to the administration of any agent, placebo or otherwise.

a. Figure 1 summarizes the results obtained in a study of 24 subjects who received 1 mg. of reserpine intravenously. The effect of intravenous saline given to 11 of these same subjects is also plotted for comparison. The

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increase in free hydrochloric acid secretion following reserpine administration was significant $p < .01$ at 60 minutes and thereafter (t test).

b. Reserpine-induced hyperchlorhydria was not influenced by methantheline bromide, 50 mg. intravenously, atropine sulfate, 0.3 mg. intravenously, or 0.4 c.c. of epinephrine 1/1000 subcutaneously, administered simultaneously with 1 mg. of reserpine intravenously.[2] These observations were made on 30 subjects in whom control studies were also performed, using 1 mg. of intravenously administered reserpine alone.

c. The effect of vagotomy on reserpine-induced hyperchlorhydria was studied in two patients, using the double blind technic. In each patient, observations of the effects of intravenous normal saline (1.0 c.c.) on gastric secretion, regular insulin (16 units), and reserpine (1 mg.) were made prior to surgery and within seven to 10 days postoperatively.

The effect of reserpine prior to and following vagotomy is graphically recorded in figure 2A. The increase in acidity induced following vagotomy is somewhat less prompt than it was prior to surgery.

Insulin (figure 2B), by comparison, produced a significant rise in gastric secretion prior to vagotomy but evoked no response following it, indicating a probable complete separation of the vagal fibers in both subjects. Saline (placebo, figure 2C) produced no significant response in either patient preoperatively or postoperatively.

Comment

These studies indicate that reserpine, in relatively small parenteral doses, is capable of inducing a significant and prolonged gastric hypersecretion. The early supposition that the gastrointestinal side-effects caused by reserpine reflected centrally induced sympatholytic or parasympathomimetic stimulation, or both,[3, 4, 5, 6, 7, 8] no longer seems tenable in view of the failure of vagotomy to modify the effect significantly.

It appears that reserpine-induced gastric hypersecretion is not dependent upon the vagal mechanism nor influenced by epinephrine. Kirsner and Ford recently presented data supporting this concept, and further indicated that this reserpine effect is not mediated through the adrenal cortex.[9]

Whether this gastric hypersecretory effect is a response to reserpine-released serotonin is not known. It is known that reserpine releases serotonin,[10, 11] and that serotonin in the unbound form can evoke gastrointestinal cramping and diarrhea.[12] However, there is no current evidence that it influences gastric secretion as well.

II. Studies with Single Oral Doses of Rauwolfia Alkaloids: The basic methods used in the following studies required that all patients be observed after an overnight fast. A Levin tube was introduced into the stomach of each subject and kept in place throughout the observation periods, which ranged from five to six hours.

As in the intravenous studies, a period for determination of baseline gas-

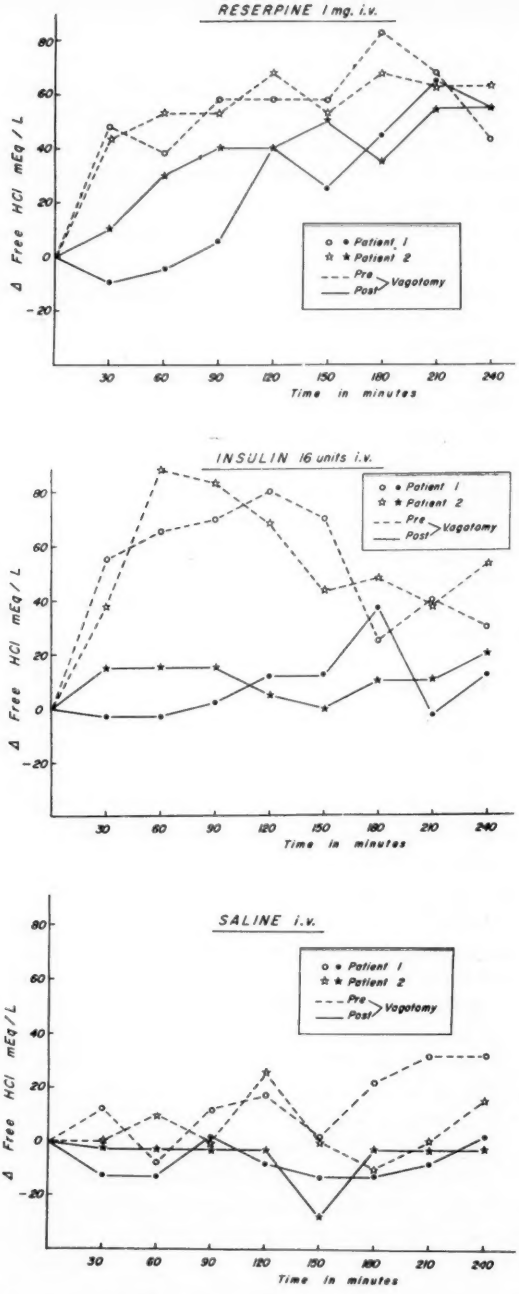

FIG. 2. Mean changes in free hydrochloric acid, before and after successful vagotomy, in two subjects, as influenced by the intravenous administration of: (A) reserpine, 1 mg., (B) regular insulin, 16 units, (C) normal saline, 1 c.c.

tric secretions was allowed prior to the administration of any agent. All compounds administered were suspended or dissolved in 30 c.c. of water prior to their administration, and an interval of 60 to 90 minutes was permitted prior to resumption of gastric juice aspiration.

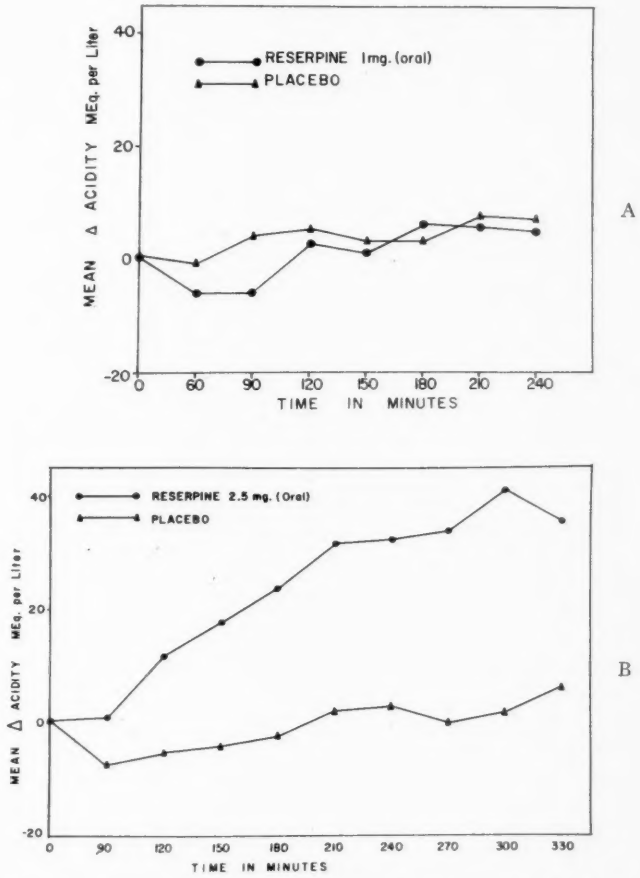

FIG. 3. Comparison of mean change in free hydrochloric acid (△ acidity) following an oral placebo and (A) oral reserpine, 1 mg., (B) oral reserpine, 2.5 mg.

Except where indicated, all of the subsequent observations were made utilizing the double blind-placebo technic, where each subject was his own control and the agents were administered by systematized randomization.

a. *Effect of 1 mg. of reserpine (oral).* As recorded in figure 3A, reserpine exerted no significant effect on gastric secretion in 17 subjects. This figure further demonstrates that an inert placebo similarly administered

to another group of patients produced almost identical results. In this study the reserpine group knew the nature of the agent administered.

b. *Effect of 2.5 mg. of oral reserpine.* The increase in gastric acidity in 31 subjects who received a single oral dose of 2.5 mg. of reserpine is illustrated in figure 3B. The increase in acidity compared to the inert placebo

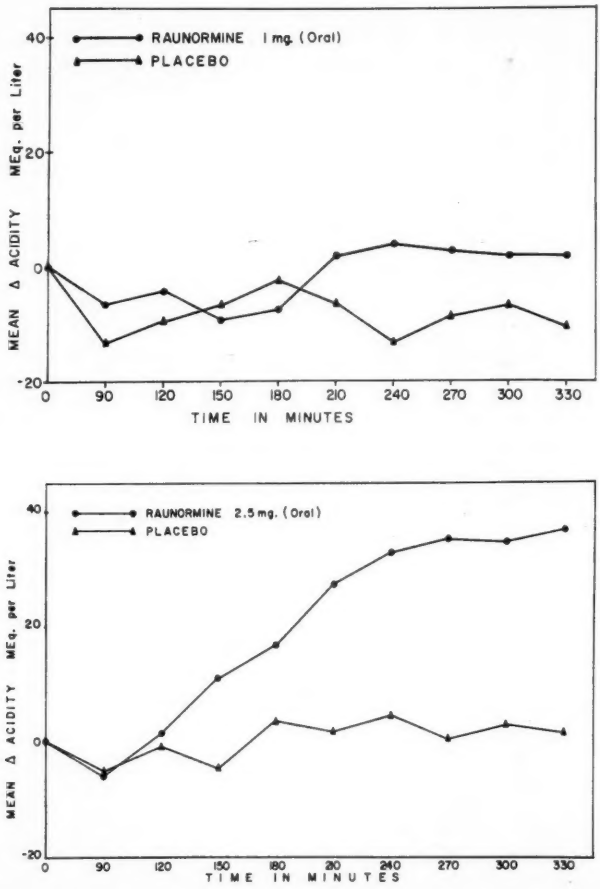

FIG. 4. Comparison of mean change in free hydrochloric acid (△ acidity) following an oral placebo and (A) oral raunormine, 1 mg., (B) oral raunormine, 2.5 mg.

effect is significant ($p < .01$) 120 minutes following drug administration and for the remainder of the period of observation.

c. *Effect of oral raunormine, 1 mg. and 2.5 mg.* Studies with the alkaloid of *Rauwolfia canescens* in 18 subjects were performed in a manner similar to those previously described. As illustrated in figure 4A, when com-

pared to the placebo, 1 mg. of this agent elicited no significant change in gastric secretory response in eight subjects. However, 2.5 mg. of raunormine produced a significant ($p < .001$) and sustained increase in gastric acidity in 10 other subjects 210 minutes following its administration (figure 4B).

d. *Effect of 100 mg. of oral* Rauwolfia serpentina. Figure 5 summarizes the results of a comparative study of the gastric secretory effects of 100 mg. of *Rauwolfia serpentina* and an inert placebo in 13 subjects. As shown, there is no alteration in gastric secretory response attributable to either agent.

Comment

Apparently single "standard" or "average" oral doses of the various Rauwolfia compounds have no effect on gastric acidity. However, the

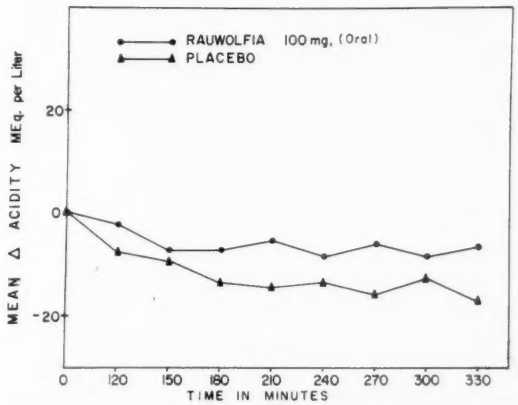

Fig. 5. Mean change in free hydrochloric acid (△ acidity) plotted for each collection period for both oral *Rauwolfia serpentina,* 100 mg., and control groups.

present studies indicate that large oral doses of these agents induce a significant and prolonged hyperchlorhydria.

Recent reports dealing with the appearance of peptic ulcer or hemorrhage in patients receiving reserpine lend support to these findings. In six cases in the American literature, the dosage of reserpine was far in excess of the suggested "standard" daily dosage of 1.0 mg. per day.[13, 14, 15]

The appearance of gastrointestinal hemorrhage in association with oral reserpine therapy has led Wofford and Cummins to advise caution when prescribing this agent in patients with peptic ulcer disease.[15] Perhaps this caution should be generally applied to all patients receiving large oral doses of the Rauwolfia alkaloids.

III. Studies with Prolonged Oral Administration of Rauwolfia serpentina *and Reserpine:*

a. *Studies with* Rauwolfia serpentina *and reserpine in normal subjects.* Nine normal volunteer subjects were observed following the determination of baseline urine uropepsin and gastric acidity levels. During a six-week period each subject received at two-week intervals, in random fashion, daily doses of reserpine, 1 mg., *Rauwolfia serpentina,* 200 mg., and a placebo similar in appearance to one of the test agents. At the end of each two-week period, gastric analysis and urine uropepsin determinations were done on all subjects. The urine uropepsin was determined by a modification of the methods of Bucher [16] and Anson [17] at a pH of 1.5 on 24-hour samples of urine.

Figure 6 illustrates the mean changes in gastric acidity and uropepsin excretion for the group. There was virtually no change in acid secretion,

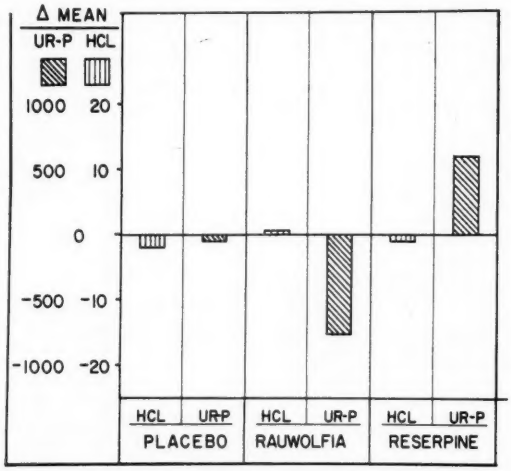

FIG. 6. Mean change (△) in free hydrochloric acid and urine uropepsin excretion in nine subjects following 14-day periods of ingestion of a placebo, *Rauwolfia serpentina,* 200 mg./day, and reserpine, 1 mg./day.

regardless of the test agent given. The uropepsin alterations are inconsistent and probably reflect the wide range of "normal" variation reported with this determination,[18] rather than a response to the test agents.

b. *Comparison of* Rauwolfia serpentina *and phenobarbital in patients with peptic ulcer disease or functional gastrointestinal complaints.* Twenty-one subjects with known duodenal ulcer or with gastrointestinal symptoms in whom other organic disease had been adequately excluded were studied by means of the double blind-placebo technic. Each subject received, in randomized sequence, for 10-day periods, four daily doses of identical-appearing tablets of phenobarbital, 30 mg., *Rauwolfia serpentina,* 50 mg., or a placebo. Daily notations of the subjective response of each patient were made throughout the study.

TABLE 1

Number of Patients Experiencing Subjective Improvement in Each Observation Period

	No. Patients	No. Patients Improved
Period 1	21	9
Period 2	21	8
Period 3	21	14

As illustrated in table 1, "improvement" was reported 31 times during the three periods of observation. However, most of the patients "improved" in the last 10-day period, regardless of the agent being administered at that time.

Table 2 records the number of patients "improving" on each agent, regardless of the period when it was administered. Nine subjects felt better while receiving the placebo, 10 while taking *Rauwolfia serpentina,* and 12 while taking phenobarbital. The differences in the responses to these agents are not statistically significant.

TABLE 2

Degree of Subjective Improvement Induced by Test Agents

	Placebo	*Rauwolfia serpentina*	Phenobarbital
Worse	0	0	0
No change	12	11	9
Improvement (mild–moderate)	9	10	12
Dramatic complete relief	0	0	0
Total number of patients	21	21	21

Side-effects, such as increased lethargy, nasal stuffiness and abdominal cramps, were noted by 13 subjects while taking the placebo. Both phenobarbital and *Rauwolfia serpentina* induced side effects in 16 subjects. The differences noted were not statistically significant (table 3).

COMMENT

The present study, dealing with nine normal volunteer subjects, indicates that neither reserpine nor *Rauwolfia serpentina* in "standard dosage" will increase gastric acidity or uropepsin excretion. These findings are in agreement with the recent reports of Kirsner and Ford [9] and Cummins and Balfour.[19]

TABLE 3

Number of Patients Experiencing Side-Effects on Test Agents

	Placebo	*Rauwolfia serpentina*	Phenobarbital
None	8	5	5
Mild–moderate	13	16	16
Severe (stop drug)	0	0	0
Total number of patients	21	21	21

The fact that patients with peptic ulcer disease or functional gastrointestinal complaints "improved" on placebo, phenobarbital and Rauwolfia with almost equal facility indicates that this improvement is probably a function of "time and attention," rather than of agent. Studies by Hagans and coworkers have demonstrated that "treatment" as such may be accompanied by significant improvement, regardless of the efficacy of the agents administered.[20] It is clear, however, that *Rauwolfia serpentina* in standard doses is not necessarily contraindicated in patients with upper gastrointestinal symptoms.

Conclusions

It is evident that Rauwolfia alkaloids, when given parenterally or in large oral doses, exert a marked stimulating effect on the gastric secretory mechanism. This effect is not noted when "usual or customary" doses of these agents are administered orally.

As therapeutic agents in gastroduodenal disease, the usefulness of small doses of the Rauwolfia alkaloids has yet to be proved. It does appear that, in patients with peptic ulcer disease or a predisposition thereto, parenteral or large oral doses of these compounds may be hazardous.

The problem of whether Rauwolfia compounds are actually ulcerogenic is not answered by these studies. Only a few cases are presently reported in whom gastroduodenal disease appeared subsequent to the initiation of reserpine therapy, despite the frequent administration of large oral or parenteral doses of these compounds to patients with various psychopathies or hypertensive crises.

The chief value of the alkaloids of Rauwolfia in gastroenterology would seem to lie in their use as a tool with which to study gastric secretion.

Summary

The various Rauwolfia alkaloids have been studied in reference to their effects on gastric secretion. Intravenously, 1 mg. of reserpine evokes a significant and prolonged hyperchlorhydria. This response is not blocked by atropine, methantheline bromide, epinephrine or vagotomy.

Oral doses of the various Rauwolfia alkaloids induced gastric hypersecretion when given in large (2.5 mg.) single doses. Small or "average" single doses of those compounds did not influence gastric secretion, however.

When *Rauwolfia serpentina* (200 mg./day) or reserpine (1 mg./day) was given over 14-day periods to normal volunteers, no significant alterations in gastric secretion or urine uropepsin excretion, as compared to a placebo effect in these same subjects, were noted.

Rauwolfia serpentina and phenobarbital were found to have no greater value therapeutically in patients with duodenal ulcer or "functional" gastrointestinal disease than did an inert placebo administered to the same subjects.

It is felt that the alkaloids of Rauwolfia exert their stimulating action on

the stomach through local rather than central activity. This activity may be mediated by serotonin.

Although no proof of their being ulcerogenic exists, it would seem *prudent* to use large doses of the Rauwolfia alkaloids with caution, especially in patients with peptic ulcer disease.

The real value of these agents, insofar as the gastrointestinal tract is concerned, seems to rest in their usefulness as a means of studying gastric secretory mechanisms.

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SUMMARIO IN INTERLINGUA

Le varie alcaloides de *Rauwolfia* esseva studiate con respecto a lor influentia super le secretion gastric. Post administration intravenose, 1 mg de reserpina evoca significative e prolongate hyperchlorhydria. Iste responsa non es blocate per atropina, bromuro de methanthelina, epinephrina, o vagotomia.

Doses oral del alcaloides de *Rauwolfia* induceva hypersecretion gastric solmente quando le doses individual esseva grande (2,5 mg). Parve doses o doses "medie" non influentiava le secretion gastric.

Quando *Rauwolfia serpentina* (200 mg per die) o reserpina (1 mg per die) esseva administrate a voluntarios normal durante periodos de 14 dies, nulle significative alteration del secretion gastric o del excretion urinari de uropepsina esseva notate in comparation con le effecto de un medication fictitie in le mesme individuos.

Esseva trovate que *Rauwolfia serpentina* e phenobarbital non esseva superior a un medication fictitie como agente therapeutic in patientes con ulcere duodenal o morbo gastrointestinal "functional."

Es opinate que le alcaloides de *Rauwolfia* exerce lor effecto stimulatori super le stomacho via un mechanismo local plus tosto que central. Il es possibile que lor activitate es mediate per serotonina.

Il existe nulle prova que le alcaloides de *Rauwolfia* es cancerogene, sed lor uso in grande doses debe esser considerate como riscose, specialmente in patientes con ulceres peptic.

Le ver valor de iste agentes—quanto al vias gastrointestinal—pare jacer in lor usabilitate como medio pro le studio del mechanismos de secretion gastric.

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THE EFFECT OF X-RAY THERAPY ON GASTRIC ACIDITY AND ON 17-HYDROXYCORTICOID AND UROPEPSIN EXCRETION *

By J. A. Rider, M.D., H. C. Moeller, M.D., T. L. Althausen, M.D., F.A.C.P., and G. E. Sheline, M.D., *San Francisco, California*

Free gastric hydrochloric acid is essential for the production of peptic ulcer. It is possible by x-radiation to decrease or even abolish production of this acid, leading to subsequent healing of the ulcer. These observations serve as the rationale for the clinical use of x-ray therapy in the management of peptic ulcer.

Since Regaud et al.[1] first studied the effect of x-ray on gastric secretion, numerous reports have indicated not only that irradiation will decrease gastric secretion, but also that, in general, the greater the exposure, the greater the decrease. In 1917 Bruegel [2] reported the use of external x-ray radiation for the treatment of peptic ulcer. Internal irradiation has been produced by agents such as P^{32}, I^{131} and radiokrypton introduced by means of intragastric balloons.[3-5] All these agents, however, are inherently dangerous, more difficult to obtain, usually require special equipment, and have other disadvantages. Therefore, the theoretically less desirable but more practical method of external x-ray radiation of the stomach has been used clinically.

Clinical Effects of X-Ray Therapy

The work of Palmer has been primarily responsible for the acceptance of x-ray therapy as a safe and useful adjunct to the medical management of peptic ulcer.[6, 7] His experience now encompasses over 20 years and includes hundreds of patients. In 1954, a five- to 17-year follow-up study of 116 patients with benign gastric ulcer who had been treated with x-ray was reported.[8] An immediate reduction of free gastric acidity of 50% or more was obtained in approximately 80% of the cases. In 36% the reduction persisted for one or more years; in the remaining patients the acidity returned to the pretreatment level within three to 12 months. In 9% an apparent permanent achlorhydria was produced. The decrease in acidity usually occurred in from four to six weeks after completion of x-ray therapy. The ulcer failed to heal in only 6.7% of patients. Forty per cent had recurrent ulcers, whereas 53.3% had had no recurrences at the time of the

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follow-up study. The over-all results also indicated a marked decrease in the incidence of complications associated with recurrences, compared to results obtained by previous medical therapy. In 1957, the results of radiation therapy were analyzed in 723 patients with duodenal ulcer who had been observed for from five to 18 years.[9] In from two to four weeks after x-ray radiation, gastric secretion was decreased by more than 50% in over one third of the cases. In half of these this effect persisted for from one to 18 years. A histamine achlorhydria developed in 12% of the total group, but was transient in most cases. Ulcers recurred in 46% of the 723 patients, but often the recurrences were less frequent and less severe than before this treatment. It is significant that in 116 cases, or approximately one third of the patients, recurrences responded promptly to a temporary resumption of a medical regimen and that no further exacerbations occurred.

Gastroscopic Changes Induced by X-Ray Therapy

Ricketts et al.[10] described the changes observed gastroscopically in 75 patients one week to three months after completion of x-ray therapy of the stomach. These changes consisted of redness and edema of the gastric mucosa, associated with hemorrhage and adherent exudate; the severity was directly proportional to the decrease in gastric secretion. Atrophy of the gastric mucosa was seen in those cases in whom permanent histamine achlorhydria developed. Schindler has reported similar findings.[11]

Histologic Changes Induced by X-Ray Therapy

The histologic effects of roentgen irradiation of the stomach and intestines in animals consist primarily of hyperemia, cellular degeneration, increased transudation and leukocyte infiltration involving all layers of the stomach. The severity of the changes is directly proportional to the intensity of the radiation. The changes in man are similar. In one study,[10] histologic specimens obtained either by biopsy or by partial gastric resection from nine patients one to 24 days after irradiation showed degeneration of occasional epithelial cells and a highly cellular, fibrin-containing exudate. The entire wall of the stomach was infiltrated with polymorphonuclear cells, plasma cells, lymphocytes, eosinophils and macrophages. In addition, the blood vessels and lymphatics were dilated; edema of the connective tissue, "fibroblast paralysis" and degeneration of lymph follicles were prominent.

In 1951, Doig, Funder and Weiden [12] were the first to correlate serial biopsies of the gastric mucosa with secretion of hydrochloric acid and pepsin in a patient with duodenal ulcer undergoing x-ray therapy. They found a lag of at least 21 days between the beginning of the treatment and the occurrence of a demonstrable reaction in the mucosa. The accumulation of "wandering cells" was densest in the superficial portion of the lamina propria. An "early, intense and long-sustained polymorphonuclear leucocyte

infiltration" was seen; the appearance of other elements was relatively slow. This inflammatory response was still present to a slight degree 353 days after cessation of x-ray therapy, by which time a virtually complete resolution of the mesenchymal cell reaction without fibrosis was present. On the thirty-eighth day after the beginning of therapy, the number of chief and parietal cells was considerably decreased. At that time the gastric tubules were greatly reduced in number and "irregularly disposed." Many of the tubular cells were mucus-secreting; only a few chief and parietal cells were present. Later biopsies showed a progressive regeneration of the gastric tubules, with the *chief cells appearing later than the parietal cells.* Free hydrochloric acid secretion decreased steadily until the forty-fourth day after treatment, when a histamine achlorhydria occurred, which persisted until the hundredth day. The achlorhydria was followed by a gradual increase in acid secretion, which, however, never returned to pretreatment levels. Estimates of gastric pepsin during histamine stimulation were somewhat inconsistent, but apparently an initial slight fall in pepsin levels gave place to a moderate rise. At the time achlorhydria was produced, however, the values for pepsin were similar to those before treatment. Following this, pepsin secretion fell rapidly to zero, but subsequently rose at a faster rate than the rise in acid; the pretreatment values, however, were never attained.

These authors stressed the fact that the fall in acid secretion preceded any demonstrable mucosal lesion; in fact, achlorhydria was present at a time when significant numbers of normal-appearing parietal cells were present. Return of acid and pepsin secretion, however, was correlated with restoration of parietal and chief cells and resolution of the inflammatory reaction. It is important to point out that there was no complete correlation between histologic changes and function, since at the time the post-irradiated gastric mucosa had returned to normal the gastric acidity and pepsin were still reduced.

A similar histologic study in three patients with duodenal ulcer was reported by Goldgraber et al.,[13] who obtained an average of 40 biopsy specimens per patient over a period of 16 weeks, by which time the fundal mucosa had reverted to normal. The onset of the histologic changes varied from five days to two and one-half weeks. These investigators concluded that the radiation has a degenerative effect initially and that the inflammatory response develops subsequently. Secretion of hydrochloric acid may be reduced before the mucosa shows histologic changes suggesting a functional disturbance. The duration of the severe reaction differed widely; it persisted for from two weeks to three months, and varied in severity from patient to patient. This variability points up unpredictable differences between patients that are probably due to inequalities in radiosensitivity.

The present study was undertaken to investigate further the effects of x-ray therapy on gastric secretion, as well as the possible relationship be-

tween gastric acidity and uropepsin and 17-hydroxycorticoid excretion. A second purpose was to determine whether the data obtained by measurement of gastric acid, uropepsin and 17-hydroxycorticoids are helpful in predicting early in the course of therapy those patients who will show a good therapeutic response.

Materials and Methods

Subjects: The study group was comprised of patients selected from our Gastrointestinal Clinic on the basis of the following criteria:

1. Evidence of a peptic ulcer (duodenal, gastric, or stomal or marginal) must be demonstrable by x-ray.

2. The ulcer must be "resistant," that is, refractory or recurrent despite adequate medical management, or because of the inability or persistent failure of the patient to follow the medical regimen.

3. Subjects must be 45 years of age or older. Patients under 45 years were accepted only if they had stomal ulcers or were considered poor surgical risks.

The 14 patients in this study met these criteria; all were given the option of x-ray therapy or surgical resection and chose the former. The group consisted of 13 men and one woman, ranging from 40 to 73 years of age, with an average of 59 years. Six patients had duodenal ulcers, five had gastric ulcers, and three had stomal ulcers.

Plan of Study: Each patient was treated by external radiation during a 12-day period. Control values for gastric acidity, urinary uropepsin and 17-hydroxycorticoid excretion were established for each patient before treatment. In several cases control values for gastric pepsin were also obtained. Frequent determinations were made in most of the patients during the time they were receiving radiation. Gastric analyses were performed at intervals of approximately three weeks, six weeks, three months, six months and one year after therapy. Uropepsin and 17-hydroxycorticoid excretion were measured more frequently, especially during the first six weeks after the start of therapy. The longest period of study was one year.

Technic of X-ray Therapy: Twelve of the 14 patients received from 1,475 to 1,700 r to the stomach within 12 days; the remaining two patients received 1,000 r within the same period. The radiation field covered the entire stomach from the cardia past the incisura. Treatment fields were rectangular in shape and varied from 10 by 10 cm. to 15 by 15 cm., with one exception, where the field was 11 by 17 cm. All treatment ports were checked by x-ray films after administration of barium sulfate suspension to the patient. The dose was delivered by 250 kvp x-ray, with a half-value layer of 2.8 mm. of copper and a target skin distance of 50 cm. Side reactions were minimal, and consisted of mild nausea in a few patients and slight, transient localized erythema. The degree of erythema, of course, varied with the thickness of the patient's body.

Gastric Analyses: The technic used for basal gastric analysis has been reported previously.[14] In addition, at the conclusion of the basal test the majority of patients received 50 mg. of Histalog injected subcutaneously, and the analysis was continued for another hour. The samples obtained were measured for volume and titrated for free hydrochloric acid. The secretion of hydrochloric acid in milligrams per hour was calculated. These values were compared with the maximal free hydrochloric acid secreted in one of the four 15-minute test periods.

Uropepsin Determinations: Determinations were performed on aliquots of 24-hour collections of urine by the method of West, Ellis and Scott,[15] with certain modifications. The exact procedure is as follows: A 2.0 ml. aliquot of urine is placed in a test tube with 0.05 ml. of 0.2% aqueous methyl orange and 0.1 ml. of 2 N hydrochloric acid. Additional hydrochloric acid may be required to bring the solution to a pH of 3 or less. (If this is done, a correction is made in the subsequent calculation for the change in volume.) The acidified urine is placed in a water bath at 37° C. for one hour. All reagents are also brought to 37° C. before use. After one hour, 0.1 ml. of the urine is transferred to a second tube, the volume is brought to 1.0 ml. with distilled water, and 1.0 ml. of acetate buffer* is added. The contents of the tube are mixed thoroughly; 0.5 ml. of milk-buffer solution† is added and quickly mixed; the tube is then returned to the water bath.

Timing: The test is timed from the moment the milk-buffer mixture is added. After one minute the tube is removed from the water bath, tilted and shaken slightly; the thin film remaining on the walls of the tube is then examined for casein particles. The tube is examined in this manner approximately every 10 seconds. The end point is reached when a fine precipitate begins to form, and the time is recorded. If the end point is reached in less than 80 seconds or more than 240 seconds, the test is repeated, using smaller or larger amounts of urine and corresponding amounts of water to bring the sample to 1.0 ml. Aliquots of 0.01 to 1.0 ml. of urine may be used. In the case of 1.0 ml. samples, the test is timed for 10 minutes before a negative report is given.

Calculation: Results are expressed in units of uropepsin excreted per hour, one unit being equivalent to 0.26 μg. of crystallized pepsin (Armour). Results are calculated as follows:

$$0.1 \times \frac{V}{v\,24} \left(\frac{100}{t}\right)^{1.32} = \text{units per hour},$$

where

V = total volume in milliliters of 24-hour urine sample,
v = amount of urine used in test in milliliters,
t = time in seconds to the end point.

* Acetate buffer: 148 ml. of a 1 molar sodium acetate solution are added to 100 ml. of 1 molar acetic acid. This results in a pH of 4.9.

† Milk-buffer mixture: equal parts of fresh homogenized milk and acetate buffer.

Gastric Pepsin: With the exception of the dilution factor, the same technic was used for determinations of gastric pepsin.

17-hydroxycorticoid Determinations: Twenty-four hour urine collections were assayed according to the method of DiRaimondo et al.[16] *

Results of Present Study

Detailed results of the effect of x-ray therapy in the 14 patients studied are shown in table 1; average values are shown in figure 1.

Effect on Free Gastric Acidity: Control basal values for free hydrochloric

Table 1

The Effect of X-Ray Therapy on Gastric Acidity and on 17-Hydroxycorticoid and Uropepsin Excretion in 14 Patients with Peptic Ulcer

Sex	Age	DX*	X-Ray Dose	Control		Maximal Free HCl Clinical Units Maximal Effect		Recovery		Uropepsin Units/Hour Maximal			17-Hydroxycorticoids Mg./24 Hr. Maximal		
				Basal	Stim.	Basal	Stim.	Basal	Stim.	Control	Effect	Recovery	Control	Effect	Recovery
M	73	DU	1700r	95	118	0	40	83	119	98	346	129	3.6	9.4	8.2
M	58	DU	1475r	61	98	0	0	0	0	38	199	6	6.2	12.7	7.6
M	54	DU	1700r	51	123	0	8	0	89	52	643	93	9.3	13.0	6.4
M	54	DU	1500r	69	95	39	78	—	—	131	732	113	10.8	12.1	7.5
M	57	DU	1500r	69	124	35	100	—	—	106	417	238	6.6	11.0	3.2
M	52	DU	1000r	60	—	0	65	—	—	70	185	—	—	—	—
M	66	GU	1500r	27	80	0	0	11	67	97	425	75	6.9	26.0	8.1
M	71	GU	1500r	0	40	—	—	—	—	32	160	36	4.3	6.4	5.0
M	67	GU	1500r	33	—	30	86	—	—	49	325	36	7.4	11.9	4.4
F	59	GU	1500r	0	90	0	0	—	—	42	128	35	4.2	7.5	5.2
M	67	GU	1000r	0	51	0	35	0	59	10	23	33	3.0	5.3	5.7
M	57	MU	1500r	51	—	32	75	—	—	70	399	67	6.6	8.2	7.7
M	40	MU	1500r	65	110	73	96	106	120	23	39	18	4.3	11.6	7.3
M	50	MU	1500r	18	68	26	30	38	76	46	65	32	7.1	12.0	6.6

* DU—Duodenal ulcer; GU—Gastric ulcer; MU—Marginal ulcer.

Maximal Effect: HCl, 3 to 16 weeks; uropepsin, 1 to 8 weeks; 17-hydroxycorticoids, 1 to 11 weeks. Recovery: HCl, 36 to 52 weeks; uropepsin, 2 to 52 weeks; 17-hydroxycorticoids, 6 to 52 weeks.

acid were established for all patients. With the exception of three subjects, values were also determined after stimulation with Histalog. In 13 patients gastric analyses were repeated at intervals from the time of therapy to the time of the last examination. (The longest follow-up period was one year from the time x-ray therapy was terminated.)

All of these patients showed a decrease in gastric acidity after x-ray therapy. The maximal fall of free hydrochloric acid as measured either by the basal test or after stimulation with Histalog occurred from three to 16 weeks after treatment. An additional gastric analysis performed 36 to 52

* The assays were performed in the Metabolic Unit for Research in Arthritis and Allied Diseases under the direction of Dr. Peter H. Forsham.

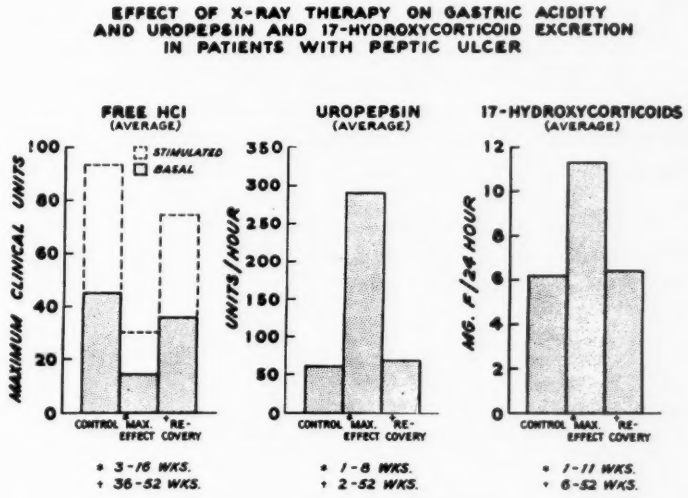

FIG. 1.

weeks later showed that the gastric acidity had not returned to the pretreatment levels in four of the seven patients followed for this length of time. The remaining three subjects, however, had never shown more than a slight reduction in gastric acidity at any time after x-ray therapy.

The average maximal fall in gastric acidity compared to the average level before treatment and at the time of the last examination is shown in figure 1.

Effect on Uropepsin Excretion: The control uropepsin levels in the 14 patients ranged from 10 to 131 units per hour, or an average of 62 units.

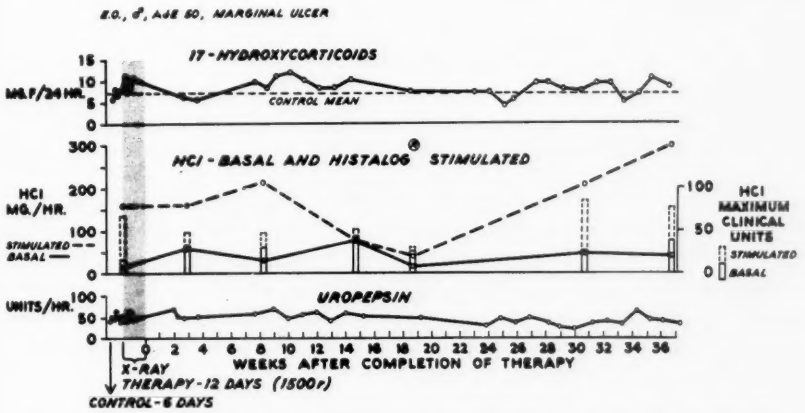

FIG. 2. *Case 1.* Effect of x-ray therapy in a representative case on the excretion of 17-hydroxycorticoids, gastric hydrochloric acid, and uropepsin.

In all cases treatment was followed by a consistent and significant rise. The maximal values ranged from 23 to 732 units per hour. The average maximal value was 292 units, an increase of 371% (approximately fivefold) over the average control value. The maximal effect occurred within one to eight weeks after therapy. The latest values, obtained from two to 52 weeks after radiation in 13 patients, ranged from 6 to 238 units per hour, or an average of 70 units. This value is almost identical with the control average of 61 units per hour for these 13 patients. Thus, the uropepsin level showed a marked initial rise, followed by a fall; in eight patients the level fell below the control value (figure 1).

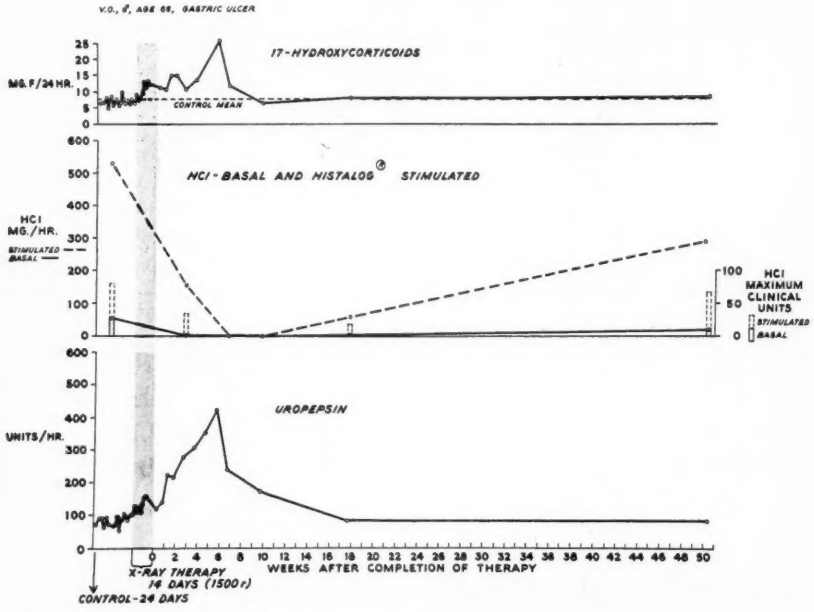

FIG. 3. *Case 2.* Effect of x-ray therapy in a representative case on the excretion of 17-hydroxycorticoids, gastric hydrochloric acid, and uropepsin.

Effect on 17-hydroxycorticoid Excretion: Control 17-hydroxycorticoid determinations were made in 13 patients. The pretreatment values ranged from 3.0 to 10.8 mg. F per 24 hours, or an average of 6.2 mg. All patients showed a rise in 17-hydroxycorticoid excretion, occurring from one to 11 weeks after completion of therapy. There was moderate fluctuation, as can be seen in the graphs of representative individual cases shown in figures 2 to 5. The average maximal value after therapy was 11.3 mg. F per 24 hours, an increase of 82% over the average control values. The range of maximal values was 5.3 to 26.0 mg. F per 24 hours. The latest determina-

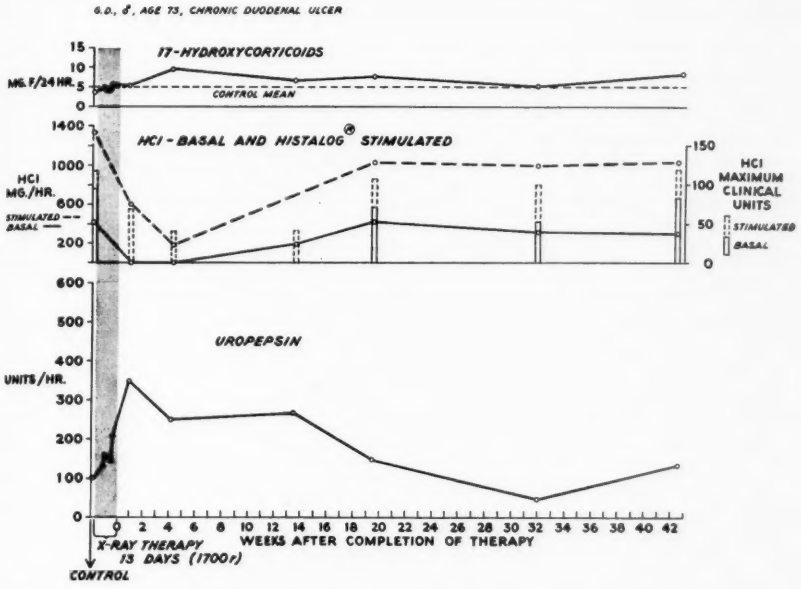

FIG. 4. *Case 3.* Effect of x-ray therapy in a representative case on the excretion of 17-hydroxycorticoids, gastric hydrochloric acid, and uropepsin.

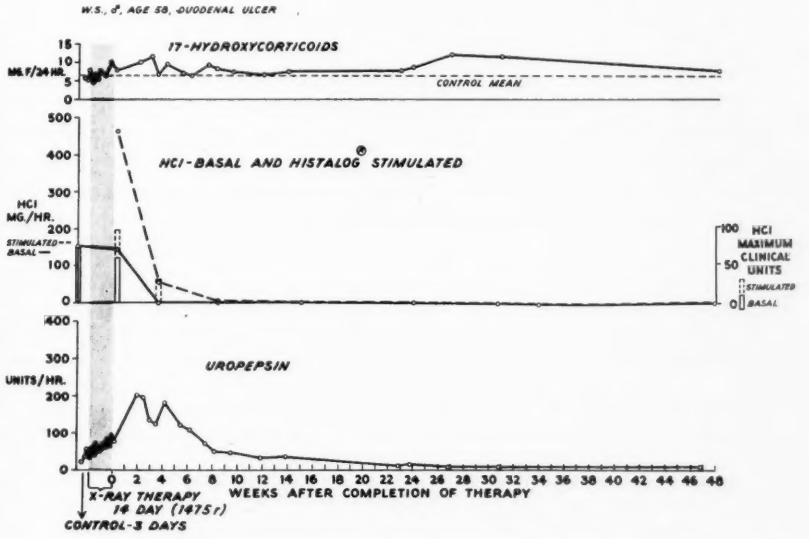

FIG. 5. *Case 4.* Effect of x-ray therapy in a representative case on the excretion of 17-hydroxycorticoids, gastric hydrochloric acid, and uropepsin.

tions were made from six to 52 weeks after termination of x-ray therapy, and ranged from 3.2 to 8.2 mg. per 24 hours, or a mean value of 6.4 mg. The average maximal rise and average pretreatment and post-treatment levels are compared in figure 1.

Case Reports

The following four cases are described in detail to illustrate characteristic responses in individual patients. The effects of x-ray therapy in these patients are shown in figures 2 through 5.

Case 1. A 50 year old male had had periodic epigastric distress since 1930. It occurred about three hours after meals and was relieved by antacids. In 1950, after the patient had a sudden hematemesis, an antacid regimen was instituted. He then was relatively well until 1952, when epigastric distress and another episode of hematemesis occurred. A duodenal ulcer was demonstrated by x-ray. A subtotal gastrectomy was performed in May, 1952. Recurrence of epigastric pain was noted one month after the operation. The patient continued to have symptoms periodically, and occasional tarry stools. In April, 1956, epigastric pain recurred, followed by a massive hematemesis. X-ray examination did not demonstrate an actual crater, but the site of the anastomosis was markedly tender. Since the patient continued to have recurrent gastric pain despite adequate medical management, 1,500 r to the stomach were administered in June, 1956. Clinically, the patient has experienced little relief of symptoms and has continued to require a strict ulcer regimen. There was no decrease in basal free hydrochloric acid; however, Histalog-stimulated gastric acidity showed a slight fall, which persisted for 19 weeks and which returned to the pretreatment level on the thirty-first week after therapy. Except for two occasions during the fifteenth and nineteenth weeks, there was little change in the quantity of hydrochloric acid secreted. The uropepsin excretion remained above the control level most of the time. The 17-hydroxycorticoid excretion showed wide fluctuations, but was usually higher than the pretreatment level.

Comment: This case exemplifies a poor clinical response and little reduction in gastric acidity. The rise in uropepsin excretion during and after x-ray therapy was minimal. It is of interest that the 17-hydroxycorticoid excretion rose during x-ray therapy, fell after therapy, showed rather wide fluctuations from week to week, but was usually higher than the control levels.

Case 2. A 66 year old man developed typical ulcer symptoms in 1949. X-ray examination of the stomach demonstrated a gastric ulcer of the lesser curvature, which healed promptly under medical treatment. In 1953 the patient had another episode of epigastric pain. X-ray studies again showed a similar ulcer. A conservative medical program resulted in complete healing of the ulcer, as shown by serial gastroscopy. Numerous cytologic studies during this time reported no malignant cells. The patient remained well until December, 1955, when he had a recurrence of epigastric pain, severe vomiting, anorexia and loss of weight. A large gastric ulcer on the lesser curvature was again demonstrated by x-ray. Because of poor medical response, the patient was given radiation in a dose of 1,500 r to the stomach in March, 1956. The response was dramatic; by the time therapy was completed the patient was asymptomatic. A bland diet and an antacid two or three times a day were prescribed, but eventually all medical treatment was discontinued.

Basal achlorhydria developed three weeks after x-ray therapy and persisted until the seventeenth week, when a slight amount of hydrochloric acid was produced. Histalog achlorhydria developed later, but did not persist so long. Both uropepsin and 17-hydroxycorticoid excretion rose at the beginning of therapy and reached a peak during the sixth week. Both values fell until pretreatment levels were reached. Four weeks after completion of the course of radiation, an upper gastrointestinal series showed the stomach to be normal. Approximately one year later the patient had a mild exacerbation of symptoms. X-ray examination showed a gastric ulcer, which responded promptly to medical management.

Comment: This case illustrates a temporary healing effect of x-ray therapy, with a subsequent recurrence which was easily treated medically.

Case 3. This 73 year old white male had had periodic epigastric pain since 1928, which occurred approximately two hours after meals and was relieved by food and antacids. On numerous occasions a duodenal ulcer crater was demonstrated by x-ray. The patient was first seen in the Gastrointestinal Clinic in 1952. In spite of good medical management his symptoms persisted and exacerbations were frequent. In May, 1956, radiation was given in a dose of 1,700 r to the stomach. A basal achlorhydria occurred during the first week after x-ray therapy, but by the nineteenth week it had returned to near pretreatment levels. At no time was a Histalog achlorhydria produced, although a decrease in response was noted. The uropepsin and 17-hydroxycorticoid excretion rose during treatment with x-ray. The peak rise in uropepsin occurred in the first week after radiation; the level gradually fell until it reached approximately the control value during the thirty-second week; subsequently there was a moderate rise. The peak of the 17-hydroxycorticoid excretion was reached during the fourth week, and with the exception of one measurement has remained elevated since that time. Clinically, the patient rapidly became asymptomatic, and has remained so. At present, his regimen consists of a bland diet and an antacid two or three times a day prophylactically.

Comment: This case illustrates an excellent clinical result, even though gastric acidity has returned to pretreatment levels.

Case 4. A 58 year old white man first noted severe epigastric pain in 1942, which was relieved by food and antacids. An upper gastrointestinal series showed a duodenal ulcer. The patient improved on conventional medical therapy. In 1954 he had a recurrence of symptoms and tarry stools; again a medical regimen was successful. In 1956 the patient had another bout of melena; again an upper gastrointestinal series demonstrated a duodenal ulcer.

Because of the repeated recurrences the patient was given a course of x-ray therapy (1,475 r delivered to the stomach). A basal achlorhydria developed in eight weeks, followed at the thirteenth week by a histamine achlorhydria which has persisted for almost a year. Uropepsin excretion rose at the beginning of x-ray therapy and reached a peak during the second week. It fell gradually until it reached control values between the twelfth and fourteenth weeks; by the twenty-third week it was below the control level. The latter effect has persisted. Excretion of 17-hydroxycorticoids also rose during the course of radiation and reached a peak during the third week. It then gradually fell, but never below the control value. By the twenty-seventh week a prolonged second rise took place. Results of the last determination are still above the pretreatment level.

Comment: This case is of special interest in that x-ray therapy produced a persistent achlorhydria which coincided with the disappearance of symp-

toms. While uropepsin showed the usual rise, the values fell to very low levels a considerable time after achlorhydria was produced. On the other hand, the 17-hydroxycorticoid excretion rose simultaneously with the rise in uropepsin excretion, and at the time of the last determination was still elevated. This patient no longer requires medical treatment.

Discussion

Many authors [1, 17-19] have considered the chief cells of the gastric glands to be more sensitive to radiation than the parietal cells. However, Miescher,[20] Doig and his associates [12] and others [2, 10, 21-26] believe that irradiation causes a prompt fall in free acidity, which is followed after a period of latency by a more gradual fall in secretion of pepsin. These findings would seem to indicate that the chief cells are less sensitive to radiation than the parietal cells. Doig reported that not only was there a latent period before the gastric pepsin fell, but also that a brief period of increased secretion followed x-ray therapy, with a subsequent fall to zero. This fall, however, occurred later than did the achlorhydria, and furthermore, the subsequent return of secretion of pepsin began sooner than the rise in gastric acidity.

In a study on the routine use of uropepsin determinations, Green and Power [27, 28] observed a higher-than-normal uropepsin value in one patient with gastric ulcer 10 days after treatment with 1,872 r to the stomach. Six days later the value was even higher. Two months after completion of therapy the uropepsin level was approximately half the first observed value; the free hydrochloric acid was also sharply reduced from its pretreatment concentration. Unfortunately, no control uropepsin values were obtained in this case.

Numerous reports in the literature indicate that a relationship exists between uropepsin and steroid excretion.[29-32] For example, steroid therapy is invariably followed by a rise in uropepsin excretion. In Addison's disease the uropepsin excretion is very low, but it is increased during administration of steroids. Little information is available as to the influence of x-radiation on excretion of steroids. French et al.[33] reported a transient rise in plasma 17-hydroxycorticosteroid levels in rhesus monkeys after total body x-irradiation, but with shielding of the pituitary and adrenals.

In the present study a consistent fall in gastric acidity was noted after x-ray therapy for peptic ulcer. Clinically, healing of the ulcer, regardless of its location, occurred in 12 of the 14 patients studied. In one patient the ulcer recurred but was much easier to manage medically than previously. In every case uropepsin excretion rose after the beginning of radiation therapy; subsequently, a fall occurred which was slower and lagged behind the fall in gastric acidity. This rise was much greater in patients in whom the secretion of hydrochloric acid was markedly reduced. These observations may be explained by an alteration in the function or the permeability

of the chief cells, leading to a change in the direction of diffusion of pepsinogen in favor of the blood stream, rather than by actual destruction of these cells. Evidence obtained from serial biopsy studies also has shown that the decrease in pepsin and acid secretion does not necessarily reflect histologic changes. This concept is further supported by the fact that simultaneous measurements of gastric pepsin and uropepsin in the two patients tested showed a definite fall in excretion of pepsin at the peak of the uropepsin elevation after radiation therapy.

The effect of x-ray therapy on the 17-hydroxycorticoid excretion appears to be more like a general stress phenomenon than a specific response to possible scatter irradiation reaching the left adrenal. In the majority of patients, excretion of 17-hydroxycorticoids returned to control or near-control levels after treatment. It is not clear why some of the patients continued to show an increased excretion after x-ray therapy.

Summary

1. In 14 patients, x-ray radiation of the stomach for the treatment of peptic ulcers resulted in a clinical remission in 12 and in a reduction in gastric acidity in all.

2. Uropepsin excretion was consistently and significantly increased during or immediately after x-ray therapy and subsequently fell approximately to control levels. This rise was much greater in patients in whom the secretion of hydrochloric acid was markedly reduced. An occasional patient showed a marked, persistent reduction.

3. The rise in uropepsin excretion after treatment suggests that radiation causes an alteration in the function or permeability of the chief cells, leading to a change in the direction of diffusion of pepsinogen in favor of the blood stream.

4. The 17-hydroxycorticoid excretion rose during and after x-ray radiation and subsequently fell toward control levels, although a few patients maintained a persistent elevation. This effect may be part of a general stress phenomenon.

5. An early marked rise in uropepsin, followed by a marked fall in gastric acidity, may enable one to predict early which patients will have the best clinical response to x-ray radiation therapy.

Summario in Interlingua

Gastric acido hydrochloric in stato libere es un condition essential pro le disveloppamento de ulcere peptic. Il es possibile reducer e mesmo abolir le production de iste acido per medio de radiation X e assi initiar le subsequente sanation del ulcere. Iste observationes forni le base theoric pro le uso clinic del therapia a radios X in le tractamento de ulcere peptic.

Esseva interprendite un studio in 14 patientes con ulcere peptic. Radiation X del stomacho como tractamento del ulceres resultava in un remission clinic in 12 del casos e in un reduction del aciditate gastric in omnes. Le excretion de uropepsina esseva

augmentate uniforme- e significativemente durante o immediatemente post le therapia a radios X, e subsequentemente illo se reduceva a approximativemente le nivellos de controlo. Le augmento esseva multo plus pronunciate in patientes in qui le secretion de acido hydrochloric esseva marcatemente reducite. In alicun patientes le reduction esseva marcate e persisteva. Le augmento del excretion de uropepsina post le tractamento suggere que le radiation causa un alteration del function o del permeabilitate del cellulas principal con un consequente alteration in le direction del diffusion de pepsinogeno in favor del circulation de sanguine. Le excretion de 17-hydroxycorticoide se elevava durante e post le radiation a radios X e descendeva subsequentemente verso le nivellos de controlo, ben que certe patientes manteneva un elevation plus persistente. Il es possibile que iste effecto es un parte de un phenomeno general de stress. Un prompte augmento de uropepsina, sequite per un marcate reduction del aciditate gastric, es un criterio pro predicer qual patientes va monstrar le melior responsas al therapia per irradiation.

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DRUG-INDUCED PEPTIC ULCER *

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Introduction

The not infrequent occurrence of peptic ulcer in man is perhaps not surprising, considering that the digestive tract, from early life, is subjected to innumerable mechanical, bacterial, chemical, thermal, physiologic, endocrinologic, neurogenic and psychogenic influences.[1] The relative significance of these factors in the development of peptic ulcer is difficult to assess; each undoubtedly is important. Individual susceptibility also plays a decisive, albeit mysterious rôle, else the incidence of peptic ulcer would greatly exceed the usual estimate of 5 to 10%.[2] The tendency of certain therapeutic agents to induce gastroduodenal ulceration represents another, increasingly important cause of peptic ulcer in man. Identification of "ulcerogenic" compounds is desirable, not only as a preventive measure but also to facilitate adequate treatment when the administration of these drugs is unavoidable. The purpose of this paper is to review recent observations concerning drug-induced peptic ulcer.

Animal Observations—Miscellaneous Compounds

The stomach and duodenum of animals are vulnerable to the local and systemic effects of many biologic compounds and medications;[3, 4, 5] these include acetylcholine,[6, 7] adrenalin,[8] insulin,[9] pitressin[10] and urecholine.[11] The lesions apparently begin as local hemorrhages, and progress, as a result of the action of acid gastric juice, to multiple erosions and superficial ulcerations, located especially in the fundus of the stomach. The ulcers closely resemble those developing in the upper digestive tract after experimental stimulation or injury to the hypothalamus and other parts of the brain.[12] Healing is rapid; chronic ulceration is rare. The ulcers have been attributed to spasm or stasis in mucosal blood vessels, causing areas of ischemia, susceptible to digestion by HCl and pepsin. The gastric ulcerations induced by pilocarpine in fasting rats have been ascribed to a similar mechanism; in this instance, mucosal ischemia may result from compression of blood vessels by excessive peristaltic activity.[13, 14, 15] The gastric hypersecretion produced by pilocarpine is suppressed by atropine; neutralization of the gastric contents with sodium bicarbonate apparently prevents the ulcerations. Mecholyl in beeswax induces prolonged gastric hypersecretion in dogs, resembling the

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response to vagal stimulation.[16, 17] The accompanying vascular engorgement presumably increases the vulnerability of the mucosa to acid-pepsin digestion. The hemorrhages and ulcerations after posterior pituitary extract are located in the acid-secreting areas of the stomach.[18, 19] Animals secreting HCl are most susceptible; neutralization of the gastric contents prevents the lesions.

The significance of these drugs as ulcerogenic agents in man is very slight or nil. The quantities prescribed clinically are much smaller than experimental doses. Nevertheless, the observations are of interest in demonstrating the importance of HCl and lowered tissue resistance in the development of gastroduodenal ulcers in animals, as in man.

Gastrointestinal bleeding, with or without peptic ulcer, has been reported after the oral intake of drugs such as Aureomycin [20, 21] and estrogens.[22] The mechanism presumably involves inflammation of the gastric mucosa, in the presence of HCl. Though these compounds are rare causes of gastroduodenal bleeding, knowledge of the possibility may clarify otherwise obscure cases.

Histamine

The injection of histamine in beeswax is capable of producing gastroduodenal ulceration in animals; guinea pigs and rats are most susceptible; rabbits and monkeys are most resistant.[23, 24, 25] The ulcers are attributable to the gradual absorption of histamine and continuous stimulation of highly acid gastric juice, acting upon the stomach and duodenum for prolonged periods. A direct vasospastic effect of histamine, diminishing the vitality of local areas of mucosa, also has been postulated. The accelerating action of nitroglycerin in beeswax upon the occurrence of histamine-ulcers has been ascribed to impaired circulation.[26] Peptic ulcer may develop in man during histamine cephalalgia [27] and after repeated injections of histamine in the treatment of multiple sclerosis [28, 29] and Meniere's syndrome.[30] These observations confirm the important rôle of HCl in the genesis of peptic ulcer. However, the hypersecretion of duodenal ulcer probably is not caused by excessive production of histamine.[1]

Caffeine

Caffeine alsó is capable of inducing gastroduodenal ulcers in cats and guinea pigs when administered in beeswax.[31, 32, 33] The lesions are ascribable to increased gastric secretion and lowered tissue resistance.[34, 35] Caffeine intravenously or by direct gastric lavage, alternating with histamine, produces vascular congestion, epithelial desquamation, multiple, bleeding erosions and ulcerations in cats.[36] The vascular changes may be comparable with the hyperemia and hypersecretion occasionally noted in the human stomach during periods of intense anxiety, hostility and resentment.[37] Caffeine acts synergistically with histamine,[38] causing prolonged and excessive stimulation of acid and pepsin secretion in many patients with duodenal ulcer.[39, 40] The

secretory effect has been attributed to direct action of caffeine upon the parietal cells.[41] The recurrence or intensification of symptoms in patients with peptic ulcer often has been ascribed to excessive consumption of coffee. Caffeine probably does not cause peptic ulcer in man, although the prolonged daily consumption of 20 to 30 grains of caffeine (equivalent to 10 or 15 cups of coffee) may be a contributory influence.[32] Caffeine-containing drugs in clinically acceptable quantities are not known to produce or reactivate peptic ulcer in man.

Adrenergic Blocking Agents

Peptic ulcer, with hemorrhage or perforation, may occur after surgical sympathectomy, undoubtedly because of vagally-stimulated hypersecretion. Tolazoline hydrochloride (Priscoline Hydrochloride) stimulates gastric secretion of acid and pepsin,[42] and therefore may be dangerous in patients with peptic ulcer; this compound, though related chemically to histamine, acts chiefly as an adrenergic blocking agent.[43] Gastrointestinal hemorrhage developed in two patients during the use of hydralazine.[44a] Peptic ulcer with bleeding recurred in a man receiving hydralazine and hexamethonium bromide for hypertension.[44b] The most likely mechanism seems to be autonomic blockade of secretory-inhibiting adrenergic impulses, allowing greater vagal influence and consequent increase in gastric secretion.

Cinchophen

Large amounts of cinchophen (2-phenylquinoline-4-carboxylic acid) given orally produce acute and chronic gastric ulcers in dogs; the incidence increases and the time interval decreases with the quantity of cinchophen.[45-50] Dogs, cats and chickens are most susceptible; rabbits and guinea pigs are resistant,[51, 52] possibly because of greater rate of bile flow.[53] The occurrence of identical lesions after the daily instillation of cinchophen into the duodenum, jejunum, ileum or rectum and after subcutaneous or intravenous infusion of a neutral salt of cinchophen suggested systemic rather than local influences, though cinchophen is excreted into the stomach after parenteral administration. The initial lesion consists of rapid destruction of mucosal cells and the development of a focal or diffuse gastritis.[54] Digestion of hemorrhagic areas by the acid-pepsin content produces multiple, acute superficial ulcerations. The erosive gastritis subsides after several weeks, and one or two chronic ulcers remain; the chronic lesions resemble the peptic ulcer of man. Similar ulcers develop in patients after excessive intakes of cinchophen.[55, 56, 57] Healing occurs promptly after discontinuance of the drug. Healing of the experimental ulcers is unaffected by liver extract, extracts of animal tissues and gastroenterostomy or vagotomy, but apparently is facilitated by vitamin D,[58] stilbestrol,[59] section of the pyloric sphincter [60] and by pectin [61] or alkalis, reducing gastric acidity.[49]

The pathogenesis of the cinchophen-ulcer has not been established con-

clusively. Though cinchophen may cause liver injury, no obvious correlation exists between the presence or absence of hepatic damage and the development of cinchophen-ulceration. Disordered motility in the region of the pylorus, release of histamine, with subsequent gastric vasoconstriction, and vague endocrinologic disturbances have been postulated. Cinchophen increases the excretion of glucuronic acid,[62] perhaps decreasing the amount of mucus, as suggested for the gastric lesions produced by camphor.[63] Destruction of the protective mucous barrier in the stomach [64] appears to be an important etiologic factor, but this effect can be explained on the basis of the gastritis. Secretory studies with cinchophen have yielded variable results. The total volume of gastric juice produced in response to histamine increased twofold during the administration of cinchophen.[47] On the other hand, acid output did not rise in dogs with Heidenhain and Pavlov pouches despite the development of gastric ulcers.[60] The location of ulcers in fundic pouches containing unbuffered acid content, and the lowered incidence of cinchophen ulcers following medical and surgical measures, decreasing acid gastric secretion,[49] nevertheless emphasize the rôle of HCl. Since cinchophen now is prescribed rarely in the management of arthritis, it retains little clinical importance as an ulcerogenic agent.

Salicylates

Salicylates have long been recognized as gastrointestinal irritants, causing heartburn and epigastric pain, ulceration of the stomach and duodenum, and bleeding.[65-74] Gastric ulceration has been induced in dogs given aspirin orally,[75, 76] and in rats after large amounts of aspirin orally or subcutaneously;[77, 78] neutralization of the gastric contents with sodium bicarbonate decreased the incidence and severity of the lesions. Hurst [79] implicated aspirin as the cause of upper gastrointestinal bleeding in approximately 50% of 58 patients. Hemorrhage in 70% of patients with duodenal ulcer was related to the use of salicylates for headache, arthritis or upper respiratory infection.[80] Perforation of peptic ulcer in seven of nine cases had been preceded by the ingestion of salicylates.[80] Kelly [81] emphasized the rôle of salicylates in 15 of 75 patients with bleeding peptic ulcer, and in 16 of 49 persons with unexplained gastrointestinal hemorrhage; a history of salicylate ingestion often was not obtained, for patients did not always classify aspirin as a drug. Many similar instances of bleeding, with or without demonstrable ulceration, have been reported. The complication may occur with small or large amounts of medication. Healing occurs promptly after discontinuance of the drug and the administration of antacids. The harmful effects of salicylates upon the gastric mucosa are not related to defective coagulation of blood, hypoprothrombinemia, or to allergic reactions. As with the preceding compounds, decreased tissue resistance in the presence of HCl appears to be the important etiologic mechanism. Patients with peptic ulcer may be more vulnerable, perhaps because of a more fragile

mucosa or a more responsive secretory mechanism. Aspirin, 1 or 2 gm. daily by mouth, stimulated gastric secretion in normal persons and in dogs;[82] the effect was noted also in dogs with isolated Pavlov pouches. Aspirin increased gastric acidity in 20 patients with peptic ulcer; in six, the gastric content promptly became bloody.[83] We[84] observed significant elevations in acidity in four of seven subjects after single oral doses of aspirin given at pH 2.8; the stimulating effect might be greater with the repeated administration of larger quantities of aspirin, approximating clinical conditions. Sodium salicylate (pH 6.0) induced a transient rise in only one of six cases. Single doses of aspirin did not cause significant eosinopenia in five patients; the acidity had risen in four of this group. The increased acidity and development of ulcerations after salicylates administered parenterally suggested a systemic influence, possibly involving the hypothalamus,[77] or the release of adrenal steroids, especially cortisone.[85] Salicylates did not reduce eosinophil counts significantly at four hours,[86] but eosinopenia has been noted at the end of six hours.[87] On the other hand, salicylates, in quantities elevating plasma levels to 38 mg.%, did not increase significantly the circulating or urinary adrenocortical steroids.[88, 89] Studies of the comparative actions of cortisone and salicylate in rats did not support the concept that salicylates act via the pituitary and adrenal cortex.[90] Smith[91] concludes that, while very large amounts of salicylates may stimulate adrenocortical function, the effects of these compounds are to be attributed chiefly to their intrinsic properties, rather than to possible endocrine influences.

Paul[92] and Caravati[93] found no gastroscopic evidence of mucosal irritation after salicylates orally or intravenously. Other observers have described inflammation, erosion and ulceration after the ingestion of salicylates. Changes ranging from mild hyperemia to submucous hemorrhage, adjacent to adherent particles of aspirin, were observed in 13 of 16 patients.[94] Among patients given salicylates two hours before gastrectomy, Muir and Cossar[83] noted mucosal irritation, including an erosive gastritis, in 12 of 20 patients given commercial aspirin. An acute erosive gastritis appeared in eight of 20 patients receiving hard aspirin tablets. The lesions were more pronounced along the lesser curvature of the stomach and in the pyloric antrum, and often took the shape of aspirin granules. Microscopic study demonstrated congestion of the mucosal capillaries, edema, cellular infiltration with polymorphonuclear and round cells, and multiple superficial erosions. In one case, half an aspirin tablet was embedded in the mucosa of the greater curvature, lying beneath the edge of an edematous, congested fold; removal of the aspirin revealed a typical appearing peptic ulcer. Among 318 patients with peptic ulcer, 110 related the symptom of heartburn to the ingestion of salicylates.[83] Approximately one third of 166 patients with hematemesis had taken aspirin within six hours of the bleeding; a similar association was elicited in 28 of 83 patients with peptic ulcer and hematemesis.[83] These observations establish salicylates as an important

cause of gastroduodenal ulceration and bleeding in man; however, in relation to the enormous quantities of salicylates taken daily, the incidence of these complications must be relatively low. The disintegration time of the salicylate tablet may be an important factor; tablets disintegrating rapidly would appear less likely than slowly dissolving preparations to irritate the gastric mucosa.

ACTH, Adrenal Steroids

General Observations: The administration of ACTH and the adrenal steroids, cortisone, hydrocortisone, prednisone and prednisolone may be complicated by the formation or recurrence of peptic ulcer, with bleeding or perforation,[95-110] and by ulcer-like symptoms in the absence of a demonstrable lesion. These complications seem to be more frequent with prednisone than with hydrocortisone,[111, 112] although the difference may be chiefly a matter of larger steroid dosage. Rothermich and Philips [113] report a low incidence of gastrointestinal problems with prednisone and prednisolone. Peptic ulcer also may complicate the steroid management of Addison's disease; [114, 115] ulcers ordinarily are rare in patients with untreated adrenal insufficiency.

The steroid-associated ulcers have been attributed to gastric hypersecretion caused by adrenocortical hyperactivity.[116] This concept suggests that physical or emotional stress activates the posterior hypothalamus, initiating a series of hormonal events, independent of neurogenic influences; these include increased output of ACTH from the anterior pituitary gland, excessive production of cortisone from the adrenal cortex and, finally, stimulation of the secretion of HCl and pepsin by cortisone and other steroids.[117] The adrenal-gastric relationship also has been postulated as a "permissive" conditioning of the acid and pepsin cells to secretory stimuli.[118]

Incidence: The frequency of steroid-associated ulcers is not known precisely. The number of ulcers in early reports appears to have been low: three instances in 79 patients given ACTH,[97] 16 cases among 360 patients receiving corticotropin or cortisone,[119] and four ulcers among 324 patients.[120] Streeten and Pollard [121] noted 21 ulcers among 730 patients. Sandweiss [122] collected 50 and Wollaeger [123] 55 steroid-associated ulcers in reviews of the literature up to 1954. More recently, Henderson [124] had recorded an incidence of 5.3% among 1,440 patients receiving cortisone. Peptic ulcer, hemorrhage and ulcer-type distress occurred in 5.1% of 4,506 individuals given prednisone; [125] the 228 patients comprising this group were distributed as follows: gastric ulcer, eight; perforated gastric ulcer, one; gastric hemorrhage, 13; duodenal and "peptic" ulcer, 32; duodenal and peptic ulcer perforated, 6; and ulcer-type distress, 168 patients. Among 885 patients collected from foreign references,[125] the incidence of peptic ulcer and related problems also approximated 5%. These figures undoubtedly do not represent all ulcers developing during steroid treatment, but they provide a reasonable approximation. The question arises as to whether these reports

reflect a significant increase in the frequency of peptic ulcer. The natural incidence of peptic ulcer in the United States usually is estimated as 5 to 10%; Doll and Jones [126] record a frequency of 6.5% for men and 2.0% for women in England; the results of autopsy surveys range from 3 to 20%.[127] In relation to these figures and to the enormous numbers of individuals receiving steroids, the incidence of steroid-associated ulcer seems low. Experience has demonstrated, furthermore, that the incidence of peptic ulcer rises with increasing interest and diagnostic attention to the problem.

The "natural" incidence of peptic ulcer in the primary diseases treated with steroids is important in evaluating the problem, but such information is scarce. Peptic ulcer may be more common than usual in rheumatoid arthritis, apart from the use of steroids; figures of 6 to 8% for the group generally,[128] and 6.5% for men and 3.0% for women [129] have been suggested. However, Kern et al.[130] found peptic ulcer in 12% of 169 patients with rheumatoid arthritis; the incidence was 2.5-fold higher than in the population at large. The impact of the chronic and often incurable disease in augmenting the susceptibility to peptic ulceration thus may be considerable. Similar surveys for other diseases treated with steroids also would be of interest in this connection. The incidence of peptic ulcer during the steroid management of rheumatoid arthritis has varied: two of 44 cases,[131] five of 64,[132] 18 of 68,[133] and 26 of 70 patients receiving prednisone [134] (37%, compared to 7% for hydrocortisone), and three of 18 patients given prednisone.[135] In contrast, many patients with rheumatoid arthritis have taken cortisone, hydrocortisone and prednisone for long periods without apparent gastrointestinal distress.[113, 136, 137, 138] Peptic ulcer also has been rare during the long-term steroid management of bronchial asthma,[139, 140, 141] various eye diseases [142] and pemphigus.[143] In our experience, the natural incidence of peptic ulcer in ulcerative colitis may approximate 10%.[144] However, we [145] noted only one instance of duodenal ulcer among 180 patients with ulcerative colitis given large quantities of ACTH and adrenal steroids for prolonged periods. A similarly low incidence of peptic ulcer during the use of steroids in ulcerative colitis has been apparent in series reported by other investigators,[146, 147] and also in regional enteritis and hepatic disease.[148]

Other Factors: The presumptive diagnosis of peptic ulcer on the basis of ulcer-type distress, such as heartburn, in the absence of a demonstrable lesion, introduces another problem, for heartburn does not necessarily signify the presence of peptic ulcer. The symptom often is associated with low or absent secretion of HCl. In a substantial number of patients with heartburn or epigastric distress during the use of steroids, roentgen studies are negative. Gastroscopic examination of patients with heartburn during steroid therapy would be of interest in demonstrating the presence or absence of gastritis or erosions, as have been noted with salicylates.

Individual susceptibility undoubtedly is an important factor. Preëxisting ulcers, hitherto quiescent, may be reactivated. On the other hand, large

quantities of ACTH and adrenal steroids may be administered to many ulcer patients without untoward effects. Thus, a man with a history of perforated duodenal ulcer requiring surgical closure later developed pemphigus and received amounts exceeding 1,000 units of ACTH intravenously, 45,000 mg. corticotropin intramuscularly, and 6,000 mg. cortisone orally, without ulcer distress. A patient with both ulcerative colitis and duodenal ulcer was given approximately 7 gm. hydrocortisone in several months, uneventfully. A male patient with duodenal ulcer and glomerulonephritis received 20 to 30 mg. prednisone daily for more than 14 months, without difficulty; one-hour basal outputs of HCl, in comparison with control observations, did not increase.

Coincidence may be involved in some instances of apparent steroid-associated ulcers. A careful history not infrequently reveals frustrating emotional problems capable of provoking peptic ulcer, in the absence of steroids.[149] Occasionally, the symptoms or bleeding antedate the use of steroids. In a 53 year old man with chronic myelogenous leukemia, gastrointestinal hemorrhage tentatively attributed to prednisone was found to have recurred intermittently since 1949. Miller and Sandweiss [150] report the perforation of a postgastrectomy stomal ulcer during steroid therapy; however, a second perforation one year later, in the absence of such medication, raised doubt as to the steroid origin of the first perforation. Machella [149] describes a patient who bled from a marginal ulcer while on steroid therapy; the bleeding was ascribed to the medication; the fact that the patient had experienced hemorrhages from the ulcer previously when he was not receiving steroids was not considered. In another case, a patient entered the hospital at 1 p.m., received one cortisone tablet at 3 p.m., and bled from an ulcer at 4 p.m. The ulcer and the hemorrhage were attributed to the single tablet of cortisone. A discriminating attitude obviously is necessary in evaluating these problems, to avoid overemphasis on steroids when other, possibly more important factors are involved and can be demonstrated by careful inquiry and observation.

Concurrent medication may represent another factor in the "steroid-ulcer" problem. Thus, in patients with rheumatoid arthritis and other musculoskeletal disorders, the administration or unsanctioned use of large amounts of acetylsalicylic acid, other salicylates and butazolidin, a procedure so routine that many patients fail to mention it in their history, may, per se, cause gastroduodenal ulceration and hemorrhage, as noted earlier. A young woman with scleroderma and arthritis, after receiving more than 90 gm. of cortisone in two years, developed a duodenal ulcer with massive hemorrhage, requiring surgery. The ulcer was attributed to the cortisone. However, she had also taken phenylbutazone and enormous quantities of salicylates, equally potent ulcerogenic compounds. Large amounts of cortisone were administered subsequently for several years, without recurrence of the ulcer, though the gastric resection had been inadequate.

The development of gastroduodenal ulcerations or ulcer-like distress is not related consistently to the duration of treatment or the total amount of steroids. Ulcers may occur within several days, several months or several years of medication. In the group reviewed by Streeten and Pollard,[121] 14 peptic ulcers developed within the first week of steroid treatment, and eight of these within the initial three days; only three appeared during the third week or later, when gastric acidity is thought to increase characteristically. In Kern's series,[130] however, the frequency of peptic ulcer paralleled the quantity and duration of steroid treatment; gastrointestinal symptoms were more likely with daily doses exceeding 50 mg. of cortisone and 15 or 20 mg. of prednisone. Bollet et al.[135] in three cases found no relationship between the length of therapy or the total steroid dosage and the development of peptic ulcer. In our experience, ulcer symptoms and hematemesis occurred in a 57 year old man with rheumatoid arthritis seven days after onset of treatment with 50 mg. of cortisone daily. On the other hand, a 34 year old woman with regional enteritis and steatorrhea developed a duodenal ulcer crater 16 months after the onset of treatment with prednisone, 10 to 20 mg. daily. The occurrence of peptic ulcer after small or large amounts of steroid would appear to emphasize the rôle of individual susceptibility.

Frequency of Gastric Ulcer: Since gastric hypersecretion is a fundamental condition of the adrenal-gastric theory, the concept would seem less applicable to gastric ulcer, characterized by normal or subnormal outputs of acid and pepsin, than to duodenal ulcer. Nevertheless, a considerable proportion of the steroid-associated lesions are gastric in location. In Sandweiss' survey, the distribution was: duodenal ulcer, 22; gastric ulcer, 12; stomal, two; and unknown, 14. Among the 55 cases collected by Wollaeger, the distribution was: duodenal ulcer, 25; gastric ulcer, 17; duodenal and gastric, two; and unknown, nine. In Kern's series of 169 patients with rheumatoid arthritis, the 21 ulcers developing in the absence of steroids were grouped similarly: duodenal, 12; gastric, eight; and site unknown, one case. The recent observations of Kammerer[151] are of unusual interest in this regard. In a routine study of the upper gastrointestinal tract in 100 unselected patients on prolonged steroid therapy, chiefly prednisone, ulcers were found in approximately 20%; almost all of them were gastric in location. Neustadt[152] noted gastrointestinal symptoms in approximately 30% of 47 patients with rheumatoid arthritis who received either prednisone or prednisolone for one year or more. Radiologic studies of the gastrointestinal tract, performed in all patients with digestive symptoms, demonstrated gastric ulcers in two instances; there were no duodenal ulcers; the lesions healed on antacid therapy without modifying the dosage of prednisone. The presence of gastric rather than duodenal ulcers might be interpreted as compatible with the absence of hypersecretion of HCl.

Healing: The "steroid-ulcer" resembles the usual peptic ulcer of man histologically and clinically. The incidence of hemorrhage and perforation

appears to be increased. Nevertheless, the ulcers heal rapidly during adequate control of acid secretion with antacids and anticholinergic drugs.[153] Our preference is for the frequent administration of calcium carbonate, with magnesium carbonate substituted as necessary to regulate bowel activity. There are numerous useful anticholinergic drugs, including Pamine, Pro-Banthine, Monodral and Antrenyl. Antacids containing aluminum hydroxide, with or without magnesium trisilicate, though helpful symptomatically, are not so potent as calcium carbonate; administered in small amounts occasionally during the day, with minimal doses of anticholinergic drugs, they cannot be expected to lower the acidity continuously and effectively in patients secreting large amounts of HCl. Thus, the prompt symptomatic relief produced by these weaker antacids, perhaps lowering the concentration of HCl only 10 or 15 units, is noteworthy. A woman with arthritis developed multiple ulcers along the greater curvature of the antrum, with bleeding, during the intake of 15 to 20 mg. of prednisone and approximately 4 gm. of acetylsalicylic acid daily. The lesions healed promptly after the administration of calcium carbonate, though prednisone, 10 mg. daily, was continued. A duodenal ulcer crater disappeared within several weeks of similar antacid treatment, despite the continued administration of steroids.

Personal Experience with Problem: Our clinical experience with the problem has been limited to a total of 14 patients, observed in the past several years, in coöperation with the arthritis, hematology and dermatology services; these do not include all instances of steroid-associated gastroduodenal complications at this hospital, but they probably represent the majority of cases seen by the gastrointestinal service. In this small group, the primary diagnoses were: rheumatoid arthritis, five; leukemia, four; steatorrhea, three; and in single cases, ulcerative colitis and scleroderma. Gastroduodenal x-rays were normal in seven, and demonstrated gastric and duodenal ulcers in three patients each; a jejunal ulcer perforated in one case; five patients gave a history of previous peptic ulcer. ACTH and hydrocortisone had been administered in single cases, cortisone in four, and prednisone in eight patients; several of this last group had received ACTH or hydrocortisone previously without digestive symptoms. One patient, a male, aged 74, is of unusual interest. The one-hour basal gastric secretion was enormous: volume, 276 ml.; acidity, 106 clinical units; output of HCl, 1065 mg. After three months of treatment with hydrocortisone (50 to 100 mg. daily), the hourly output of acid was 1043 mg., and one month later, 1,357 mg.; hydrocortisone was discontinued soon thereafter. In the absence of steroids, nine and 10 months later, the one-hour basal secretion was the highest we have observed: 1,639 and 1,612 mg., respectively. After four days of treatment with prednisone, 20 mg. daily, the patient required surgical closure of a perforated jejunal ulcer; the pH of jejunal aspirates was highly acid. The patient during the subsequent 16 months has taken 20 to 30 mg. prednisone daily, without gastrointestinal distress.

Gastric Secretion: Gastric secretion during the administration of ACTH and the adrenal steroids in man has been measured only occasionally. Six normal subjects, one patient with gastric ulcer and one with duodenal ulcer [116] were reported as having had increases in the basal and nocturnal outputs of HCl and pepsin; the elevations were not apparent until after several weeks of treatment with ACTH. According to Carbone et al.,[154] the one-hour basal secretion rose in normal young men given 40 mg.

TABLE 1

Basal Gastric Secretion during Period of Ulcer or Ulcer-Like Distress during Steroid Therapy

Patient	One Hour Output HCl (mg.)	Steroid
J. E. 459910 Gastric ulcer	60, 63	ACTH
J. S. 260019 Ulc. colitis	79	Prednisone
S. R. 592845 Ulc. colitis, duod. ulcer	39	Hydrocortisone
M. W. 517872 Rheum. arthritis-gastric ulcer	43, 5	Cortisone
E. M. 635242 Arthritis	28	Prednisone
M. M. 673928 Steatorrhea	11	Prednisone
O. M. 557582 Lymphoma	4	Prednisone
J. K. 663105 Arthritis-gastric ulcer	3	Prednisone
E. M. 206868 Arthritis	0	Cortisone
A. F. 654531 Myelogenous leukemia, large gastric rugae	0	Prednisone
G. R. 603197 Lymphatic leukemia	0, 0	Cortisone
Standard Values for Comparison		
Normal	84	304 men
Gastric ulcer	51	15 pts.
Duodenal ulcer	202	173 pts.

prednisolone daily for one week; the anticholinergic drug, oxyphenonium, inhibited the response. The "prednisone-effect" was attributed theoretically to enhancement of the action of acetylcholine upon the parietal cells. More adequate control measurements of gastric secretion would have been desirable in both studies. In our laboratory, single average doses of corticotropin intramuscularly or cortisone orally did not stimulate gastric secretion in man. Basal secretion rose in two individuals with gastric ulcer during the use of ACTH. However, in three additional ulcer patients the gastric response

to histamine was unchanged after corticotropin therapy for several weeks. The one-hour basal secretion measured in 11 patients experiencing ulcer or ulcer-like symptoms during steroid therapy was normal or low in each instance (table 1). In one patient with heartburn, gastroduodenal x-rays were normal and no HCl was demonstrable in the gastric content; thus, the heartburn, initially ascribed to "steroid-ulceration," actually was attributable to some other cause. We also found considerable variation in the basal secretion of HCl measured repeatedly in the same person, in the absence of medication.[155] The pattern of acid output (high, medium or low), rather than percentile changes for one or two hours, appeared to be a more valid index of significant trends. With these more stringent criteria, the pattern of the two-hour basal secretion did not rise significantly in nine of 10 patients with ulcerative colitis given large amounts of corticotropin, hydrocortisone or prednisone and observed for periods of up to 60 weeks.[156] * Gastric secretion increased in one case after six weeks of ACTH therapy, remained elevated for nine weeks, and then declined to original levels, despite the continuation of ACTH for a total period of 42 weeks; emotional tension arising from the consideration of colectomy was important in this patient at that time and might have accounted for the temporary rise in secretion. Dreiling [157] observed no change in the volume, acidity or enzyme output of the gastric contents in normal persons and in patients with gastric or duodenal ulcer given ACTH, hydrocortisone or prednisolone intravenously. Hirschowitz and his co-workers [158] studied the eight-hour gastric responses to ACTH, hydrocortisone, corticosterone, prednisone and aldosterone in normal subjects. ACTH induced a slight rise, but insignificant in comparison with the response to histamine; the plasma pepsinogen was unchanged. Aldosterone evoked the most striking increase in urinary pepsinogen. The decrease in visible mucus and viscosity of the gastric content during the use of ACTH was of interest. Kammerer and Rivelis [159] found that hydrocortisone, prednisone or prednisolone, given orally for five or more days, did not elevate the output of HCl or pepsin significantly in patients with rheumatoid arthritis, some of whom had had an active peptic ulcer during steroid therapy; viscosity diminished slightly; uropepsin excretion did not change appreciably.

Gastric secretory studies in animals also have varied considerably. Villarreal et al.[160] observed, after a latent period of four or five hours, increases in acid, pepsin and chloride in dogs with intact stomachs, vagally-denervated pouches and with the antrum removed, given ACTH intramuscularly; this trend was not apparent in adrenalectomized animals. Basal gastric secretion and the responses to histamine and methacholine increased in female dogs with Heidenhain pouches after prednisone intravenously.[161] In pylorus-ligated rats Welbourne and Code [162] observed no significant rise

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in gastric acidity or in the frequency of ulceration after cortisone. Initial studies by Zubiran, Dragstedt and their colleagues [163, 164] demonstrated a slightly elevated secretion in dogs with various types of gastric pouches; however, the increases were considered insufficient to produce gastroduodenal ulceration in animals. Recently, in dogs with Pavlov, Heidenhain and total gastric pouches, ACTH (40 to 80 units), subcutaneously and intramuscularly, cortisone (200 mg.) intramuscularly, and hydrocortisone (50 mg.) intravenously, did not stimulate gastric secretion.[165] Prolonged administration of cortisone did not increase gastric secretion significantly in dogs with Heidenhain pouches; [166] acidity rose during the use of cortisone when the antrum was excluded but retained; this effect was attributed to loss of the acid-inhibiting mechanism of the antrum. Hollander and his co-workers [167] were unable to demonstrate significant increases in the gastric secretion of dogs with Heidenhain pouches and complete antrectomy after 40 units of ACTH intramuscularly. Neustadt [152] cites studies in which 50 mg. of cortisone, administered intramuscularly daily to two dogs with Dragstedt-pouches for two to three months, after a control period of the same duration, did not increase the volume of secretion or output of HCl.

The data in man and animals and our findings thus indicate that, while the output of acid and pepsin may rise during the administration of ACTH and the adrenal steroids, gastric secretion in the great majority of cases is not increased. Factors other than hypersecretion appear to be involved in the gastric ulcers or ulcer-like distress encountered during steroid therapy. In subsequent studies of this problem, careful attention should be directed to the pronounced spontaneous variations in acid secretion in man. At least three and possibly five analyses are desirable to establish a valid control pattern for comparison with the effects of drugs given for prolonged periods. Much of the emphasis upon increased gastric secretion during steroid therapy is based upon elevations in urinary pepsinogen. A direct correlation may exist between gastric pepsin and urinary pepsinogen under carefully controlled conditions, when analyses are repeated at least three times during the same period.[168] Single determinations of urinary pepsinogen under ordinary clinical conditions may vary considerably and do not necessarily reflect gastric secretory activity accurately.[169] Simultaneous measurement of gastric acid and pepsin and of urinary pepsinogen during steroid therapy in patients hospitalized under metabolic control conditions is required to clarify this relationship.

Adrenocortical Function: Adrenocortical function in peptic ulcer has been measured only occasionally. Turner,[170] on the basis of subnormal eosinophil responses to epinephrine and ACTH, postulated stress and then exhaustion of the pituitary-adrenal mechanism. Diminished pituitary-adrenal activity in peptic ulcer has been reported by several investigators.[171, 172, 173] Sandweiss [174] found normal outputs of 17-ketosteroids and subnormal values for 11-oxycorticoids in the urine of patients with peptic ulcer; however, the dif-

ferences are not impressive. Rozenbojm et al.[175] reported high levels of 17-hydroxycorticoids in the plasma and urine of patients with duodenal ulcer; the response to ACTH intramuscularly was considered excessive. On the other hand, Freeman [176] and Cummins et al.[177, 178] found normal values for plasma corticoids in duodenal ulcer, and the responses to ACTH gel or ACTH intravenously were normal. Further studies of this problem with more precise measures of adrenal function are desirable.

"Hyperadrenal" Diseases: On the basis of the pituitary-adrenal-gastric hypersecretion theory, a high incidence of duodenal ulcer might be expected, a priori, in diseases with adrenocortical hyperactivity. Evidence of such a relationship has not appeared thus far.[179] Kyle [180, 181] found excessive gastric responses to a gruel meal in patients with Cushing's syndrome; adrenalectomy lowered the acidity to normal. The acidity was high in most patients with elevated 17-hydroxycorticosteroid excretion. However, increased gastric secretion often was associated with normal or zero excretion of corticoids. None of the 11 patients in Kyle's series had peptic ulcer, a fact noted also by other investigators.[179] We observed a gastric ulcer in a woman with clinical findings compatible with post-traumatic hypopituitarism. The ulcer was resected in 1953; the lesion histologically was identical with the usual benign ulcer. In 1954 the patient developed clinical signs of Cushing's disease. The urinary excretion of 17-ketosteroid excretion was elevated. However, basal and histamine gastric secretions were normal. The low incidence of peptic ulcer in Cushing's disease, if confirmed, would tend to further diminish the possibility of adrenocortical hyperfunction as a primary mechanism in the usual peptic ulcer. Perhaps there are fundamental, as yet unidentified, qualitative and quantitative differences in adrenocortical activity between the endogenous adrenocortical hyperfunction of Cushing's disease and the exogenously-produced hyperadrenalism of steroid therapy.

Tissue Resistance: The normal or unchanged gastric secretion during steroid therapy and the considerable number of gastric ulcers, with normal or low outputs of acid, suggest the role of diminished tissue-resistance in the pathogenesis of the steroid-associated ulcer. The decreased viscosity of the gastric content during the administration of ACTH [182] is of interest in this connection. The effect of adrenal steroids upon the resistance of the stomach and duodenum to acid-pepsin digestion has not been studied sufficiently. The apparently favorable therapeutic results with ACTH and cortisone in dogs with Mann-Williamson operations and in patients with duodenal ulcer,[183] and with ACTH and cortisone in the control of recurrent gastric hemorrhage,[184] are unusual, inasmuch as most investigators have dealt with deleterious rather than beneficial effects of steroids upon the digestive tract. Prednisone did not delay the healing of mucosal and serosal wounds in the stomach of mice.[185] In contrast to the negative results reported with corticotropin and cortisone in guinea pigs,[186] prednisone and prednisolone had

an "ulcerogenic" effect, in the ileum as well as in the stomach and duodenum of guinea pigs.[187] ACTH and cortisone apparently increased the number of gastric ulcerations in rats.[188] Mainardi [189] found that cortisone and prednisone did not influence the volume of secretion in pylorus-ligated rats; single, very large doses (5 mg. per kilogram of body weight) increased the incidence of gastric ulceration. ACTH and cortisone did not produce gastric ulceration in rabbits, but increased the area and the depth of pitressin gastric ulcers.[190] Cortisone in doses of 2.5 and 10.0 mg. per kilogram had no effect on the healing rate of 5 mm. wounds in the stomachs of dogs, but prolonged the healing time of 10 mm. wounds.[167] Clinically, Forbes [191] reported delayed healing of gastric ulcer, as judged by x-ray, after ACTH; cortisone did not delay healing. We [192] also noted slow healing in several patients with gastric ulcer given ACTH. However, uninterrupted and complete healing of gastric and duodenal ulcers has been observed subsequently. Much more investigation of the cellular and tissue responses to the adrenal steroids will be required before the pathogenesis of the steroid-associated ulcers can be elucidated fully.

There is thus information interpreted as implicating the hypothalamus, pituitary gland and the adrenal cortex in the stimulation of gastric secretion and the development of gastroduodenal ulceration in man. The concept appears plausible, but the evidence at present does not seem conclusive. Nevertheless, the association between steroids and peptic ulcer or ulcer-like distress appears to be significant, perhaps on the basis of tissue injury.

Butazolidin

Butazolidin (phenylbutazone), 1,2 diphenyl-4-butyl 3,5 pyrazolidinedione, a nonsteroid, synthetic compound, prescribed in the management of certain types of arthritis and musculoskeletal disorders, may induce the development or recurrence of peptic ulcer, with bleeding and perforation.[195-208] The complication may occur after intramuscular and rectal as well as oral administration. It is not correlated consistently with the duration of treatment or the total amount of Butazolidin; ulceration and bleeding have occurred within several days of therapy or after several months. In two instances, gastric ulcers perforated after two and four intramuscular injections, respectively.[204, 205] The incidence of Butazolidin ulcers is not known precisely, but the complication is not rare. Mauer,[209] in a survey of 3,934 patients treated with Butazolidin, reported 40 proved cases of peptic ulcer; an additional 424 individuals developed digestive symptoms, including epigastric pain. Hillemand and Cocovanis [210] described nine additional cases of gastric ulceration, with and without hemorrhage. Kern et al.[211] noted a slightly higher incidence of peptic ulcer, among patients with rheumatoid arthritis, in those receiving Butazolidin than in those given steroids or salicylates. Gastric symptoms with bleeding were noted in 15% of 55 patients; [212] peptic ulcer was estimated to have developed or recurred in at least

10 of 200 cases, not including those with ulcer-like distress or with occult blood in the feces, in whom x-rays were normal.[213]

Butazolidin also may produce ulceration of the stomach and duodenum, with perforation, in rats [214, 215] and in both normal and adrenalectomized dogs after prolonged intramuscular injection.[216] Diffuse gastritis, hemorrhagic duodenitis, multiple erosions and superficial ulcerations have been observed in animals and in patients. In a woman of 75 who had died of hemorrhage after 1,200 mg. Butazolidin daily for eight days, the stomach contained approximately 100 superficial ulcers, lying in parallel rows on the ridges of the gastric rugae.[217] The phenylbutazone and cinchophen ulcers are similar in that both develop as a sequel to gastritis and duodenitis; both may occur after parenteral as well as oral administration. Cinchophen ulcers tend to localize in the stomach near the pylorus, whereas Butazolidin ulcers are more common in the duodenum. The erosive gastritis and duodenitis, and destruction of the mucus-secreting cells, undoubtedly diminish the resistance of the stomach and duodenum. In addition, gastric acidity may increase after Butazolidin administered orally or intramuscularly. The acidity rose significantly in 30 of 57 studies with single oral doses of 200 to 600 mg., and in 10 of 32 tests with 50 to 400 mg. intramuscularly.[84] The more frequent increases after oral administration probably are related to the more rapid and more complete absorption from the gastrointestinal tract. Similar elevations in gastric acidity were noted in five patients with duodenal ulcer who had undergone vagotomy and gastroenterostomy, indicating that the gastric effect does not require an intact vagal mechanism. The stimulating effect of Butazolidin upon gastric secretion has been confirmed by other investigators.[218]

Butazolidin apparently does not increase adrenocortical activity.[219] Single doses of the drug orally and intramuscularly did not lower eosinophil counts significantly. Furthermore, the acidity increased after Butazolidin orally in three of five patients who had had bilateral adrenalectomy and oophorectomy for carcinoma of the breast.[84] A similar increase has been noted in a completely adrenalectomized dog. The gastric stimulating effect of Butazolidin thus may involve a local irritant action upon the parietal cells; it does not appear to require adrenocortical hyperfunction. The importance of HCl in the development of the Butazolidin ulcer is illustrated by the course of a 61 year old man with severe rheumatoid arthritis who had experienced ulcer distress initially in September, 1950. Symptoms recurred in January, 1951, after 800 mg. cortisone; a large gastric ulcer healed after several months of treatment with calcium carbonate. Severe ulcer distress recurred in August, 1952, October, 1952, and in May, 1953, after small amounts of Butazolidin; gastric acidity rose in each instance. Roentgen irradiation of the upper two thirds of the stomach produced complete anacidity. Butazolidin and cortisone subsequently were resumed without further ulcer distress.

Reserpine

Reserpine, the crystalline ester alkaloid of *Rauwolfia serpentina,* prescribed in the management of hypertension and certain emotional disorders, is well tolerated when taken by mouth in comparatively small doses.[220] Large amounts may produce or reactivate peptic ulcer, with bleeding and perforation.[221-225] Hussar and Bruno [226] described three instances of duodenal ulcer developing for the first time during the prolonged oral administration of 3 to 6 gm. of reserpine daily. Though the incidence of this complication is not known, it appears to be low. Stimulation of gastric secretion is an important factor in its development. Reserpine intravenously increased the output of HCl in dogs with Heidenhain pouches.[227] In man, reserpine intravenously stimulated gastric secretion within 30 minutes, the effect continuing for at least four hours; the failure of anticholinergic compounds to inhibit the response suggested a humoral or peripheral action.[228, 229] Single doses of 5 mg. of reserpine intramuscularly increased the HCl output; [230] the prior injection of atropine reduced the volume response but not the acidity. The reserpine effect was attributed to stimulation of the sympathetic inhibitory centers in the hypothalamus, or of the diencephalon-inhibiting cortical nerve impulses. The rise in gastric secretion after 2.5 mg. reserpine parenterally in patients without basal HCl after vagotomy, or vagotomy and sympathectomy, suggested a direct influence upon the parietal cells.[231] Reserpine orally in quantities of 1.0 or 1.5 mg. reportedly increased the output of HCl.[232] In other studies, oral doses of 2.5 mg. stimulated gastric secretion, but much less than after intravenous injection; [229] single doses of 0.5 mg. increased gastric secretion.[233] Negative results were obtained in patients with gastric or duodenal ulcer given 1.0 mg. daily for periods approximating six weeks.[234] We [235] noted a moderate rise in basal secretion in only one of eight normal persons receiving 1.0 mg. by mouth daily for 12 weeks. On the other hand, reserpine intravenously, 1.0 to 2.5 mg., evoked tremendous rises in acid output, both in normal persons and in patients with duodenal or gastric ulcer. Comparative studies with single intravenous doses of hydrocortisone (50 mg.), corticotropin (20 mg.) and reserpine (1.0 to 2.5 mg.) indicated little effect with the steroids during a period approximating eight hours, whereas the secretion after reserpine was enormous. A similar response in patients with duodenal ulcer who had undergone vagotomy and gastroenterostomy indicated that the effect did not require an intact vagal mechanism.

The role of the adrenal cortex in the action of reserpine is unsettled. Very large amounts (5 mg.) apparently stimulated adrenocortical function in dogs.[236] Children treated with reserpine were thought to respond excessively to ACTH, though renal excretion of 17-hydroxycorticoids did not increase appreciably; [237] however, in three monkeys maintained on reserpine for nine days, the output of steroids rose. We found no significant eosinopenia despite tremendous stimulation of gastric secretion with small amounts

of reserpine. Large amounts of reserpine orally and intramuscularly did not increase the 24-hour output of urinary pepsinogen.[238] Furthermore, reserpine intravenously stimulated gastric secretion in an adrenalectomized dog with a Thomas pouch, as in normal dogs.[239] The reserpine effect thus does not appear to require adrenocortical stimulation. Central inhibition of sympathetic influences and correspondingly augmented parasympathetic activity may be implicated, though reserpine increases gastric secretion in patients with vagotomy and in dogs with vagally denervated pouches. The endogenous release of histamine may be a factor,[240, 241] but antihistaminic drugs, while eliminating the flushing, malaise and headache induced by reserpine, do not suppress the secretory response.[229, 230] The observations that serotonin intravenously does not stimulate gastric secretion, and that its precursor, 5-hydroxytryptophane, inhibits acid output,[242] suggest that serotonin is not involved in the gastric response. Present evidence thus indicates that reserpine orally, in amounts of up to 1.0 mg. daily, may be prescribed with little risk of stimulating gastric secretion and reactivating peptic ulcer. Large doses orally or reserpine intravenously may be hazardous in patients with a known or suggestive history of peptic ulcer.

Comment

Peptic ulcer results from failure of the gastroduodenal mucosa to withstand the digestive action of acid gastric juice. Though the fundamental cause remains obscure, two mechanisms are of paramount importance: the presence of HCl in the gastric content, and lowered resistance of the stomach and duodenum. Studies on the possible etiologic role of gastritis and duodenitis, vascular abnormalities, nutritional and tissue deficiencies, endocrine, neurogenic or psychogenic disturbances relate ultimately to these two factors. In duodenal ulcer, excessive production of HCl and pepsin appears to be the dominant influence. In gastric ulcer the secretion is normal or low; diminished tissue resistance seems to be the primary factor, though acid is essential to the process. The mechanism of the gastric hypersecretion in duodenal ulcer is not understood completely, but seems to be chiefly neurogenic or vagal in origin. The causes of decreased tissue resistance also are not clearly defined; presumably they concern the protective mucus barrier of the stomach, the regenerative capacity of the mucosa, the vascularity of the mucosa and perhaps intracellular enzyme systems.

Drug-induced peptic ulcers also develop on the basis of acid-pepsin digestion of vulnerable areas in the gastroduodenal mucosa. Gastric secretory stimulation predominates for some compounds, such as Mecholyl, Priscoline, histamine and reserpine. The ulcers developing under these circumstances result from the continuous and prolonged contact of excessive amounts of HCl with the stomach and duodenum. Vascular congestion, stasis and spasm, diminishing the vitality of local areas of mucosa, probably contribute to the formation of the lesions.

Lowered tissue resistance is of primary importance in the ulcerogenic effects of other drugs, including cinchophen, salicylates and Butazolidin, though HCl participates in the process. The initial and major effect of cinchophen, salicylates and Butazolidin upon the gastrointestinal tract seems to be the development of a severe hemorrhagic and erosive gastritis and duodenitis. The inflammation lowers tissue resistance by destruction of the epithelium, especially the mucus-secreting cells. Gastric acidity increases, perhaps as a result of local irritation of the parietal cells. Drugs or procedures neutralizing or lowering the secretion of HCl diminish or prevent the lesions. Adrenocortical hyperfunction is not necessarily involved in the secretory effects of salicylates or Butazolidin. The ulcerogenic properties of caffeine appear to include both the tissue and acid components. Experimentally, caffeine causes severe vascular congestion and mucosal irritation; gastric secretion increases, perhaps by direct action on the parietal cells.

The ulcers complicating the use of ACTH and the adrenal steroids seem to represent a more complex process. The validity of the hypothesis implicating the hypothalamus, pituitary and adrenal system would appear to depend upon the demonstration of increased quantities of circulating steroids in the blood, and the presence of hyperadrenalism and gastric hypersecretion in patients with steroid-associated ulcers, as well as in those with naturally occurring peptic ulcer. However, the output of HCl, as has been demonstrated, usually is not increased significantly, either immediately or during the prolonged administration of large quantities of ACTH and the adrenal steroids, in patients with ulcerative colitis, normal persons or patients with peptic ulcer. Variations in technic and in control standards may account for the occasional divergent results. The considerable proportion of gastric ulcers among the gastrointestinal complications of steroid therapy also would be compatible with normal or low outputs of HCl, rather than hypersecretion. Thus, while acid and pepsin production may rise in occasional individuals receiving steroids, this apparently does not occur in the great majority of patients. The development of distress within several days of the onset of steroid treatment, preceding the presumed characteristic late rise in gastric secretion, the prompt relief of pain by relatively weak antacids, the disappearance of symptoms despite continued steroid treatment, and the uneventful resumption of steroids after a previous ulcer or ulcer-like episode, likewise do not seem compatible with significant hypersecretion. While studies in dogs reportedly have demonstrated a rise in acid and pepsin production after ACTH or prednisone, most investigators have been unable to demonstrate significant increases in HCl and pepsin, despite intensive steroid administration. Estimates of gastric acid and pepsin production by the measurement of urinary pepsinogen may be inadequate, since single analyses, obtained under ordinary clinical conditions, do not reflect gastric secretory function accurately or consistently. Repeated measurements of urinary pepsinogen in patients maintained under metabolic conditions in the hospital are

required for this purpose; under these circumstances also there may be divergent results.

There also is no agreement concerning adrenal function in peptic ulcer. While increased levels of circulating and urinary steroids have been reported by some investigators, others have not obtained satisfactory evidence of hyperadrenalism. The infrequency of peptic ulcer in diseases characterized by adrenocortical hyperfunction, such as Cushing's syndrome, tends to support the view that adrenocortical hyperactivity is not a primary mechanism in the usual peptic ulcer of man.

The normal or low secretion of HCl during steroid therapy, the substantial number of gastric ulcers, the increased incidence of hemorrhage and perforation, perhaps indicative of rapidly penetrating lesions, and the occasional perforations elsewhere in the digestive tract suggest the importance of lowered tissue resistance in the pathogenesis of the lesions. Steroids may increase the vulnerability of the stomach and duodenum to experimental ulceration in animals; the nature of the effect is not known. Decreased fibroplasia in ulcers or induced wounds may be observed early in the course of steroid treatment; healing may be slowed but the delay is not permanent. The possible deleterious effects of adrenal compounds upon the normal or intact stomach and duodenum apparently have not been studied.

The etiologic relationship of peptic ulceration or gastrointestinal bleeding to the medication is not always clear or readily established. The lesions complicating the use of salicylates or Butazolidin develop soon after the onset of treatment, occasionally within six to 12 hours. The prompt chronologic association, together with the known ulcerogenic properties of these compounds, is persuasive, albeit circumstantial, evidence of the relationship. The ulcers complicating the use of large amounts of reserpine similarly appear to develop under circumstances which define clearly the etiologic association. There also seems little reason to doubt the relationship of the adrenal steroids to some of the ulcers complicating treatment. However, in view of the many irritant influences upon the gastrointestinal tract of man, and the frequency of peptic ulcer generally, are all ulcers developing during the prolonged administration of steroids attributable to these compounds? Perhaps other factors also require consideration: the incidence of peptic ulcer in the diseases treated with steroids; the apparently increased incidence of peptic ulcer in rheumatoid arthritis, in the absence of steroids; the frequent presence of serious emotional problems, and the concurrent administration of other ulcerogenic drugs, such as salicylates and Butazolidin. Careful appraisal of each case is necessary, therefore, to evaluate accurately the relationship of the steroids to gastroduodenal ulcer or ulcer-type distress. Not all ulcers developing during the use of the adrenal compounds are steroid in origin.

The importance of individual susceptibility in the development of drug-induced peptic ulcer is indicated by the occurrence of the complication in a

relatively small proportion of cases, and by the variable correlation between dosage or duration of treatment and the development of the lesion. Patients with a preceding history of peptic ulcer would appear to be more vulnerable. This tendency has been emphasized with salicylates, Butazolidin and, to some extent, with the adrenal compounds. However, many ulcer patients receive large amounts of "ulcerogenic" drugs without difficulty, and individuals having recovered from drug-induced ulcer may resume therapy uneventfully; the factors involved are not known.

The frequency of drug-induced peptic ulcer is difficult to ascertain from the literature. In this connection, it is of interest that the sales of antacids, anticholinergic drugs and proprietary preparations for gastric distress in this country approximate $80,000,000 per annum.[125] Digestive symptoms, ulcer distress and bleeding are not uncommon during the use of aspirin and other salicylates; in some series the incidence of gastrointestinal complications may range as high as 30 to 70%. Gastroduodenal ulceration, bleeding and perforation also occur frequently during the administration of Butazolidin. In Mauer's review, the combined incidence of established peptic ulcer and digestive symptoms approximated 12%. The incidence of gastrointestinal complications during the use of ACTH and the adrenal steroids also is difficult to determine precisely. Many cases undoubtedly are not recorded in the literature. On the basis of published reports and the analysis of large numbers of cases, Henderson has estimated the incidence of peptic ulcer and ulcer-type distress as approximately 5 to 6% for cortisone and for prednisone. This figure parallels the accepted general incidence of peptic ulcer in this country. In relation to the huge numbers of patients receiving steroids, the incidence of ulcer complicating steroid therapy appears to be relatively low.[243] On the other hand, the frequency of the complication is not inconsequential, and the reports in the literature are too numerous to be disregarded. Present evidence thus indicates a direct relationship between the steroids and at least some of the gastroduodenal ulcerations complicating their use. The nature of the association is not clear at present. As in the function of all other organs and cells in the body, an intact adrenal cortex seems essential to normal gastric function. However, this relationship, applicable to many systems, does not necessarily connote adrenocortical hyperfunction as the cause of gastric hypersecretion in man. Adrenocortical hyperfunction or gastric hypersecretion is not demonstrable, except in a relatively small number of susceptible individuals. The adrenal-gastric hypersecretion theory, furthermore, does not account for the development of gastric ulcer or ulcer-like distress with low or normal basal gastric secretion during steroid therapy. Decreased resistance of the gastroduodenal mucosa to acid-pepsin digestion may be the most significant factor in the development of "steroid-ulceration." This important phase of the problem deserves further study.

The present survey thus demonstrates the potential ulcerogenic proper-

ties of numerous drugs. The hazard seems greatest with compounds prescribed in the management of rheumatoid arthritis and musculoskeletal disorders, namely, salicylates, Butazolidin and ACTH and the adrenal steroids; it seems to be less with reserpine. In addition to such factors as the nature of the compound, the dosage and the duration of treatment, individual susceptibility to drug-induced peptic ulcer contributes a decisive but unpredictable influence. Excessive administration of ulcerogenic drugs obviously is undesirable. Effective control of the gastric acidity with diet, antacids and anticholinergic medication is indicated when the use of these compounds seems unavoidable. Fortunately, the lesions usually respond promptly to adequate antacid therapy. Consideration of the possibility of drug-induced peptic ulcer should aid in preventing serious gastrointestinal problems, permit effective treatment of complications, and perhaps clarify the cause of otherwise obscure gastrointestinal distress and bleeding.

Summary

The administration of certain therapeutic agents may be complicated by the development or reactivation of peptic ulcer, with hemorrhage and perforation. The mechanisms involved are not understood completely, but they undoubtedly include stimulation of gastric secretion and decrease in the resistance of the gastroduodenal mucosa locally. The gastric and duodenal ulcerations observed experimentally after Mecholyl are attributable to excessive gastric secretion resulting from vagal stimulation, although vascular effects may be involved. Priscoline and other adrenergic blocking agents cause an increase in gastric acidity indirectly, chiefly by suppressing inhibitory sympathetic nerve impulses, permitting greater vagal activity. Histamine is capable of producing or reactivating peptic ulcer as a result of the tremendous direct stimulation of gastric acidity. Cinchophen may cause peptic ulceration after oral or parenteral administration, presumably as a result of gastritis or duodenitis, although other factors, including increased gastric secretion, may be implicated. Gastrointestinal bleeding, in patients with and without peptic ulcer, not infrequently is related to the ingestion of aspirin. Salicylates may increase gastric acidity, perhaps as a result of direct stimulation of the parietal cells. Vascular congestion, hemorrhages, erosions and superficial ulceration have been observed in areas of gastric mucosa in direct contact with aspirin.

The administration of ACTH and the adrenal steroids also may be complicated by the development of peptic ulcer and ulcer-type distress. Hemorrhage and perforation are not uncommon. Many of the ulcers are gastric in location. Symptomatic relief and healing occur with antacid therapy, despite continued steroid therapy. The incidence of this complication seems comparatively small in relation to the large number of patients receiving steroids. Not all lesions occurring during the administration of adrenal steroids are attributable to the medication; other etiologic factors include

those responsible for the natural incidence of peptic ulcer generally and in the diseases treated, emotional problems and concurrent ulcerogenic medication, such as aspirin and Butazolidin. Gastric secretion does not increase in most cases during the immediate or prolonged administration of very large quantities of ACTH and adrenal steroids. Adrenocortical hyperfunction does not appear to be a primary mechanism in the usual peptic ulcer of man. Nevertheless, the administration of ACTH and the adrenal steroids has been followed by a significant number of ulcers; lowered tissue resistance may be the most important factor.

Butazolidin orally or intramuscularly increases the concentration of HCl occasionally, and may cause reactivation of peptic ulcer, with hemorrhage and perforation. The gastric secretory stimulating effect is observed in patients with vagotomy and in individuals with bilateral adrenalectomy. Inflammation of the gastric mucosa, with direct stimulation of parietal cells, may be an important mechanism. Reserpine orally, in dosages of 1 mg. daily, usually does not increase gastric secretion; however, daily quantities of 2 mg. or more may elevate the volume of secretion and gastric acidity. This rise is especially pronounced following reserpine intravenously, and may occur in patients with vagotomy and in the absence of significant eosinopenia. The secretory effect may be due to central suppression of inhibitory sympathetic nerve impulses or to the endogenous secretion of histamine. Excessive secretion of serotonin probably is not involved. The drug-induced increases in gastric secretion and reactivation of peptic ulcer in occasional patients only suggest that individual susceptibility is an important factor determining the tendency to peptic ulcer.

Summario in Interlingua

Le administration de certe agentes therapeutic es a vices complicate per le disveloppamento o la reactivation de ulcere peptic con hemorrhagia e perforation. Le mechanismos interessate non es completemente comprendite, sed illos include sin dubita le stimulation del secretion gastric e le reduction local del resistentia del mucosa gastroduodenal. Le ulcerationes gastric e duodenal que esseva observate post le administration experimental de Mecholyl es attribuibile al excesso de secretion gastric que resultava de stimulation vagal, ben que il es possibile que effectos vascular es etiam implicate. Histamina pote producer o reactivar ulceres peptic como resultato de su tremende stimulation directe del aciditate gastric. Cinchophen pote causar ulceration peptic post administration oral o parenteral, presumibilemente como resultato de gastritis o duodenitis, ben que altere factores—incluse le augmento del secretion gastric—pote etiam esser implicate. In patientes con e sin ulceres peptic, sanguination gastrointestinal es relationate non infrequentemente al ingestion de aspirina. Salicylatos pote augmentar le aciditate gastric, possibilemente como resultato de un stimulation directe del cellulas parietal. Congestion vascular, hemorrhagias, erosiones, e ulceration superficial ha essite observate in areas de mucosa gastric que esseva in contacto directe con aspirina.

Le administration de ACTH e del steroides adrenal pote etiam esser complicate per le disveloppamento de ulcere peptic o de gravamines ulceroide. Hemorrhagia e perforation non es incommun. Multes del ulceres es gastric secundo lor location.

Alleviamento symptomatic e resanation occurre in consequentia de therapia antacidic, in despecto de continuation del therapia steroide. Il pare que le incidentia de iste complication es comparativemente basse si on considera le grande numero de patientes qui recipe steroides. Non omne le lesiones que occurre durante le administration de steroides adrenal es attribuibile al effectos del medication. Altere factores etiologic que pote afficer le situation es—a parte omne illos responsabile pro le incidentia natural de ulceres peptic in general e in le ambiente del morbos sub tractamento—le presentia de problemas emotional e le uso concomitante de medicamentos ulcerogene, per exemplo aspirina e Butazolidina. Le secretion gastric non se augmenta necessarimente durante le acute o prolongate administration de multo grande quantitates de ACTH e de steroides adrenal. Hyperfunction adrenocortical non pare esser inter le mechanismos primari in le caso usual de ulcere peptic in humanos. Nonobstante, le administration de ACTH e del steroides adrenal ha essite sequite per un numero significative de ulceres. Le reducite resistentia del histos es possibilemente le factor le plus importante.

Le administration oral o intramuscular de Butazolidina augmenta a vices le concentration de HCl e pote esser responsabile pro le reactivation de ulcere peptic, con hemorrhagia e perforation. Le effecto stimulatori super le secretion gastric es observate in patientes con vagotomia e adrenalectomia bilateral. Inflammation del mucosa gastric, con stimulation directe del cellulas parietal, es possibilemente un mechanismo importante. Reserpina oral in doses de 1 mg per die non resulta usualmente in un augmento del secretion gastric, sed quantitates diurne de 2 mg o plus es capace a elevar le volumine del secretion e del aciditate gastric. Iste augmento es specialmente marcate post administrationes intravenose de reserpina e pote occurrer in patientes con vagotomia e in le absentia de grados significative de eosinopenia. Le effecto secretori es possibilemente le resultato de un suppression central de inhibitori impulsos de nervo sympathic o del secretion endogene de histamina. Il non es probabile que excessos in le secretion de serotonina es implicate. Le augmentos pharmacogene del secretion gastric e le consequente reactivation de ulcere peptic in certe patientes suggere solmente que susceptibilitates individual es un factor importante inter illos que determina le tendentia a disveloppar ulceres peptic.

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POSTBULBAR DUODENAL ULCER *

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POSTBULBAR duodenal ulcer, as the name implies, is one situated in the duodenum distal to the duodenal bulb. Anatomically, such an ulcer is in the postbulbar part of the first portion, or in the second, third or fourth portion, of the duodenum. Fewer than 150 cases have been reported in the English literature in this century, the largest series being that of 18 cases reported by Swarts and Rice [1] in 1954. This type of ulcer may be extremely difficult to diagnose, inasmuch as specific diagnostic criteria have not been universally accepted. The purpose of this investigation was to determine in a large series of cases whether ulcers of this nature deserve special recognition from both a clinical and a therapeutic standpoint. The position of the ulcer far out in the duodenum may often prevent easy roentgenographic demonstration on routine examination.

Anatomists have divided the duodenum into four major components. Roentgenologists agree with this subdivision, but in actual practice they see many normal variations in contour, length and course, especially of the first two portions. These variations were well described by Ball and coworkers.[2] They pointed out that in some patients the duodenal cap has its apex at the superior duodenal flexure, or junction, of the first and second portions, while in others the cap is often much shorter and comprises, perhaps, only half of the entire first portion of the duodenum. Thus, from the roentgenologist's point of view, the first portion of the duodenum often has two subdivisions: the cap, or bulb, and the postbulbar portion, which is the more variable structure of the two (figure 1). Hence, one should not think of "first portion" and "cap" as synonymous, nor, conversely, should one think that a postbulbar ulcer necessarily is in the descending limb.

Furthermore, inflammatory lesions of the duodenum are prone to cause hypercontractibility or "irritability," and when the lesion is situated at or beyond the apex of the bulb the spasm may be sufficiently severe and constant to alter the normal anatomic characteristics of the whole region. In the present study we considered ulcers occurring beyond what was considered to be a normal duodenal cap.

The roentgenologic diagnosis of duodenal ulcer distal to the cap is

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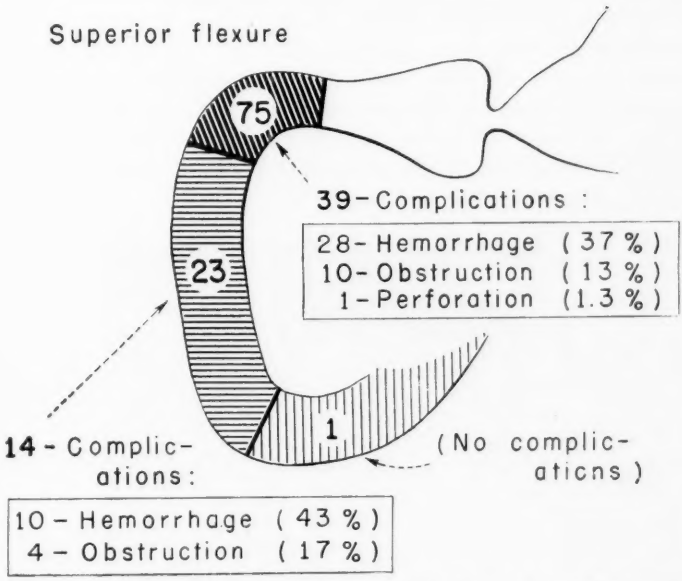

FIG. 1. Location of 99 postbulbar duodenal ulcers and incidence of complications according to site of origin.

predicated on the same basic pathologic changes that are found in ulcer of the cap, and is based on the constancy with which these changes can be observed by fluoroscopic and roentgenographic examination. The most characteristic sign, of course, is the presence of a crater (figures 2 and 3). This

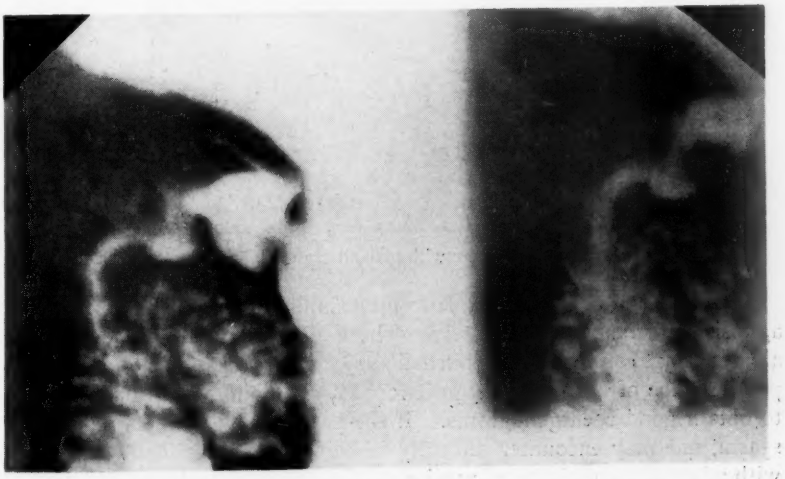

FIG. 2. Postbulbar duodenal ulcer with a large crater. There was a history of symptoms for three weeks.

niche may appear to be fairly shallow or very deep, depending upon the degree of penetration into the duodenal wall. It is accompanied by variable degrees of duodenal deformity, largely due to spasm in the vicinity, but probably due also to edema, or cicatrization, or both. Often there may be an incisural type of deformity opposite the ulcer crater, presumably due to an eccentric reflex contraction. Concentric narrowing, with or without obvious obstruction, may also occur (figure 4).

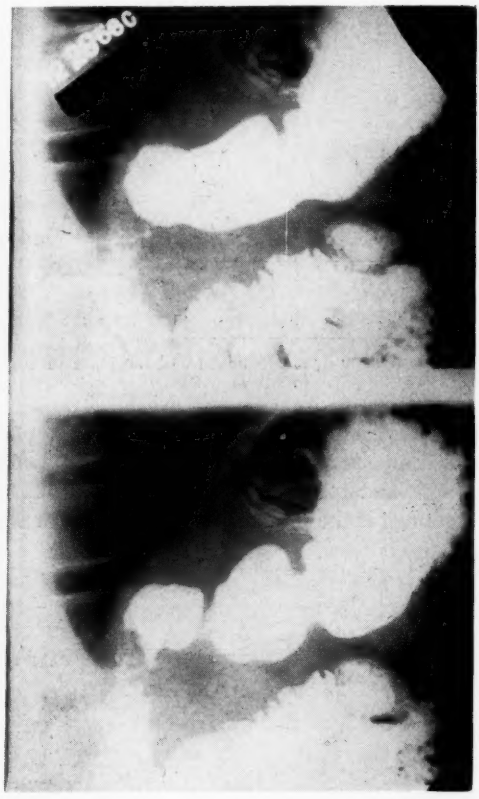

FIG. 3. Postbulbar duodenal ulcer with a small crater in second portion of duodenum.

Close attention during fluoroscopic examination is mandatory if the diagnosis is to be made accurately. The distal part of the duodenum is not always easy to study, even in normal subjects, as peristaltic activity may propel the bolus of barium through it rapidly. This may also make it difficult to obtain good roentgenograms. If the patient has some degree of pylorospasm, one may encounter difficulty in being able to distend the duodenum with a large enough bolus of medium. At times it may be necessary to place

the patient in a prone right oblique position to overcome these difficulties and to obtain a longer look at the structure. Reëxamination may also be required to arrive at a final diagnosis. The roentgenologist may easily overlook a small lesion if the examination is difficult technically, or is hurried.

Material and Observations

In this series of 99 cases, there were 86 men and 13 women, giving a ratio of about seven to one. The average age at the time of diagnosis was 50, the range being 20 to 74 years. Symptoms began as early as the age of 10 and as late as the age of 69. The outstanding clinical symptom was ab-

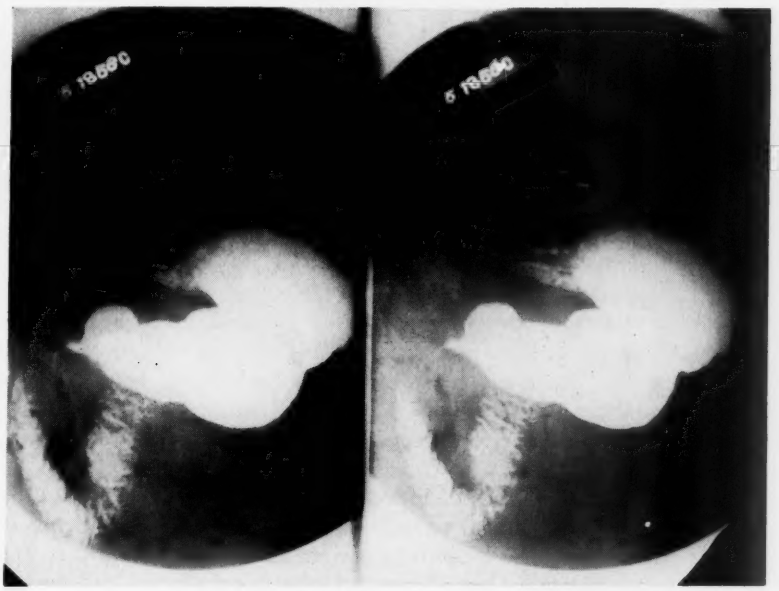

Fig. 4. Postbulbar duodenal ulcer with obstruction.

dominal pain, which occurred in 83 patients. Typical ulcer pain, characterized by an intermittent aching, gnawing or burning sensation in the upper part of the abdomen that occurred usually one or two hours after eating, that often awakened the patient from a sound sleep, and that was relieved by food or alkali, was present in 67 patients. The remaining 16 patients had pain suggestive but not completely typical of the pain of duodenal ulcer. Sixteen of the 99 patients experienced no pain whatsoever.

Of the 83 patients who had pain, 60 had epigastric pain alone, and 14 had epigastric pain in combination with discomfort in the right upper quadrant. Seven patients had pain in the right upper quadrant alone, and one

each had pain in the left upper quadrant and in the lower part of the abdomen. Twenty-eight specifically mentioned that the pain extended straight through to the back, and in one instance it extended to the right lower quadrant. Forty-nine patients denied definite extension of pain. Night distress severe enough to awaken the patient from a sound sleep was specifically mentioned in 46 of the 83 patients with pain.

An outstanding feature of these 99 cases of postbulbar duodenal ulcer was the high incidence of complications. Foremost among these was gastrointestinal bleeding, which occurred in 38 patients. Sixteen patients had hematemesis on one or more occasions, while 37 patients had one or more episodes of melena; 15 had both hematemesis and melena. Only four of the 38 patients did not have pain associated with their bleeding.

Clinical and roentgenographic evidence of obstruction was present in 14 patients. The obstruction proved to be almost complete in four instances. Slight hyperbilirubinemia occurred in two of this group, but clinical jaundice

TABLE 1

Results of Treatment of Postbulbar Duodenal Ulcer

Result	Treatment	
	Medical	Surgical
Asymptomatic or improved	37	16
Same	9	2
Worse	10*	2
Treatment too recent, or no follow-up	16	
Death from unrelated causes	7	
Total patients	79	20

* Nine treated surgically later.

was not detected. Free perforation of the ulcer was the initial symptom in one patient.

Physical examination was of little or no value in establishing the diagnosis. Mild upper abdominal tenderness was present in 38 patients. In only four patients was the tenderness periumbilical in location.

Of the many laboratory procedures carried out, only the results of gastric analysis appeared to be significantly abnormal. The values for free hydrochloric acid ranged from 12 to 94 clinical units in the 75 patients in whom the acid was determined. Thirty-eight patients, or 50%, of these had values of more than 50 units. Only five had values of less than 20 units.

The presence of a postbulbar duodenal ulcer was demonstrated by roentgenographic examination in all 99 cases. As previously mentioned, the roentgenographic diagnosis is often difficult, but in 65 of the cases the ulcer was demonstrated at the time of the first examination. It was necessary, however, to have a second examination in 30 cases, and a third examination in four cases, before the ulcer was visualized. The severity and organic nature of the symptoms prompted the clinician to request these repeated roentgenographic examinations.

The incidence of complications of postbulbar duodenal ulcer by site of occurrence is given in figure 1.

Seventy-nine of the patients were treated by a medical regimen. The remaining 20 had symptoms or complications of such severity that an immediate operation was performed.

Follow-up of the 79 medically treated patients revealed that 10 were asymptomatic, 27 definitely improved, nine unchanged, and 10 definitely worse (table 1). Nine of the last-mentioned 10 patients had symptoms of such severity that they eventually required surgical treatment. In 16 patients no follow-up was possible, or the follow-up period was too short to be significant, and seven patients died of unrelated causes.

Of the 20 surgically treated patients, 15 underwent partial gastric resection and five gastroenterostomy. Postoperative complications included subdiaphragmatic abscess in two patients and thrombophlebitis in one. Prolonged follow-up revealed marginal ulceration in four patients; in one of these gastrointestinal bleeding occurred, and in another a gastrocolic fistula eventually developed. A fifth patient had gastrointestinal bleeding without demonstrable evidence of recurrent ulceration. There were no immediate postoperative deaths.

Discussion

The present series of 99 cases of postbulbar duodenal ulcer, added to those reported in the English literature, brings the number of acceptable cases to more than 200. It is difficult to arrive at the exact incidence of this type of ulcer, as it rarely is tabulated separately in clinical reports. At this time, it can be said only that in the 25-year period represented by this study of Mayo Clinic material, there were only 99 cases of postbulbar duodenal ulcer, this being an extremely small percentage of all cases of duodenal ulcer. This low incidence is at variance with the incidence usually cited in necropsy studies. It is to be expected that in the latter studies a higher incidence would be found, as it is apparent that some ulcers are clinically quiescent. The incidence of these ulcers found at postmortem examination ranges from 5%, as reported by Portis and Jaffé,[3] to 17%, as reported by Sturtevant and Shapiro.[4] The small number of cases reported in the literature makes it difficult to compile any significant data as to age and sex. It is apparent from the present study that this kind of ulcer may appear at any age, but there is a definite predisposition for it to occur in males.

A brief perusal of the literature makes one aware of the marked difference of opinion regarding the symptomatology of this unusual ulcer. In the present study we attempted to establish the clinical and roentgenographic criteria for diagnosis, and to reconcile the divergence of opinion reflected in the present literature. It soon became apparent that most patients (84%) presented a history fairly typical of duodenal ulcer. The type, location and extension of the pain were practically identical with those of the more com-

mon duodenal ulcer. In spite of the absence of initial positive roentgenographic findings in 34% of the cases, the clinical history was so suggestive of a duodenal ulcer that the clinician felt the need for further x-ray studies, which disclosed the postbulbar duodenal ulcer.

In the past, complications of postbulbar duodenal ulcer have been considered to occur much more often and to be more severe than are those of the usual duodenal ulcer. The most common complication of any type of duodenal ulcer is gastrointestinal bleeding. It has been stated by Ivy and co-workers,[5] and also by Morlock,[6] that the incidence of bleeding from duodenal ulcer is between 20 and 25% in peptic ulcer patients admitted to a hospital. Balfour [7] said that this same percentage is true of ulcer patients followed for 10 years. The incidence of hemorrhage associated with postbulbar duodenal ulcer ranges, according to reports, from 37% [8] to as high as 72%.[1] In the present series, 38 patients had at least one episode of gastrointestinal bleeding, and 28 of these had more than one episode. According to Borman, Wolke [9] stressed the high incidence of gastrointestinal bleeding in the absence of pain in this type of ulcer. This situation occurred in only four patients in the present series.

The second most common complication of any type of duodenal ulcer is pyloric obstruction. Ivy and co-workers [5] said that some form of cicatricial obstruction occurs in 20% of cases of duodenal ulcer, and is severe in 16%. This agrees with the finding of obstruction in 14% of the patients with postbulbar duodenal ulcer who were included in the present series.

Perforation of a postbulbar duodenal ulcer apparently is rare. The occurrence of only one perforation in this series is in agreement with the incidence of perforation observed by Swarts and Rice.[1] It is significant that the perforation occurred as the earliest symptom of duodenal ulcer. Medical management of this unequivocal perforation was successful, and after convalescence the postbulbar duodenal ulcer was demonstrated for the first time. The location of these ulcers seems to predispose to penetration into the neighboring organs, rather than to free perforation into the peritoneal cavity. In this series, definite penetration into the pancreas, with the formation of an inflammatory mass, was noted on five occasions at operation. Involvement of the common bile duct in such a mass secondary to a penetrating postbulbar duodenal ulcer has been mentioned in the literature. This has resulted in a clinical picture suggestive of obstructive jaundice.[10] On no occasion was there any clinical evidence of jaundice in the present group of patients.

The incidence of serious complications in men in this series (55%) was greater than that observed in the usual series of duodenal ulcer (table 2). Gastrointestinal hemorrhage alone accounted for this increased incidence. On the other hand, the women in this series exhibited about the same incidence of complications as might be expected from ordinary duodenal ulcer. There has been some speculation that the incidence of complications is higher

in the second portion of the duodenum than in the other postbulbar portions. In the present series there was no significant relationship between location of ulcer and incidence of complications (figure 1).

Much concern has been expressed recently about the relationship between peptic ulcer and the administration of various steroid hormones. In two patients of this series this unusual duodenal ulcer appeared to have followed such therapy. The first patient, a 47 year old white woman whose condition previously had been diagnosed as psychogenic rheumatism and functional dyspepsia, was admitted to the hospital because of melena and hematemesis. A complete history revealed that the bleeding followed recent administration of steroids for the rheumatic pains. Although previous x-ray examinations of the upper part of the gastrointestinal tract had not disclosed any evidence of an ulcer, it is not possible to state dogmatically that there was a definite causal relationship between the steroids and the peptic ulcer. The difficulty of demonstrating postbulbar duodenal ulcer has been emphasized

TABLE 2
Complications of Postbulbar Duodenal Ulcer According to Sex

Complication	Postbulbar Ulcer (99 Cases)				Usual Ulcer, Per Cent
	Women (13 Cases)		Men (86 Cases)		
	Number	Per Cent	Number	Per Cent	
Hemorrhage	4	31	34	40	20–25
Obstruction	1	8	13	15	16–20
Perforation	1	8	0	—	3–13

previously and may well apply here. At least it seems reasonable to assume that the steroids may have reactivated a previous ulcer. The second patient had primary biliary cirrhosis without historical or roentgenologic evidence of duodenal ulcer. After the intravenous use of corticotropin and prednisone for intense pruritus, abdominal pain not typical of that seen with duodenal ulcer and a massive gastrointestinal hemorrhage were first noted. A postbulbar duodenal ulcer was demonstrated at fluoroscopic examination. It responded well to a medical program and the cessation of hormonal therapy.

In radiologic diagnosis, errors of omission are more frequent than errors of commission on the part of the radiologist, as shown by the necessity for reëxamination in a significant percentage of cases. Certain conditions must be distinguished from peptic ulcer. In the first place, one must approach the examination with an objective attitude, and not with a determination to find a cause for the patient's symptoms, for the latter attitude may lead one to commit positive errors by assigning undue pathologic value to anatomic variations. An anomalous course of the second portion of the duodenum,

when in the form of a tight coil, or distortion of it by a previous operation on structures in the vicinity, may be mistaken for deformity due to ulcer.

Cholecystitis may induce a secondary deformity of the distal portion of the duodenum which can closely simulate that produced by an ulcer in either the distal part of the cap or the second portion. If the clinician indicates to the radiologist the results of any recent cholecystographic study or any previous biliary operation, the radiologist is in better position to evaluate an atypical duodenal deformity.

A perforating ulcer penetrating into the head of the pancreas may produce an inflammatory mass that roentgenographically simulates a pancreatic neoplasm with secondary duodenal involvement. The presence of a crater and the nature of mucosal involvement often help to distinguish these two conditions. Pancreatitis also may distort the duodenum and at times be difficult to distinguish from primary duodenal ulcer. A duodenal diverticulum, when seen in the proper plane, is typical but, if seen only en face, can appear to be a barium-filled crater.

The management of patients with postbulbar duodenal ulcer deserves special consideration because of the apparent high incidence of serious complications. It seems reasonable to treat these patients with a medical regimen much as one treats patients with the usual type of duodenal ulcer. When such a regimen is embarked on, however, it is important that both the physician and the patient be aware of the serious complications that may develop. The literature suggests that medical regimens have been unsuccessful or infrequently used because of the difficulty of making a correct diagnosis. In the majority of cases, the presence of a postbulbar duodenal ulcer has not been established until complications requiring surgical treatment have occurred. In the present series of 99 patients, however, 79 were initially started on a medical regimen, and long-term follow-up revealed that 37 were asymptomatic or definitely improved, nine remained unchanged and 10 were definitely worse; nine of the last-mentioned 10 patients required surgical treatment eventually. More success with medical treatment may be anticipated when the physician and the patient are completely aware of the high incidence of complications and the need for following the regimen more rigidly. Also, earlier diagnosis of this type of ulcer, before serious complications occur, will allow improved medical management.

Surgical treatment has consisted of essentially the same type of operation as that usually recommended for the more common type of duodenal ulcer. Thus, 15 patients in the present series underwent partial gastrectomy with a Polya type of anastomosis, and five patients underwent simple gastroenterostomy; there were no immediate postoperative deaths. There is some evidence that postoperative morbidity is increased, but the smallness of the number of patients treated surgically makes this observation of doubtful significance. Six patients had had multiple operations in an attempt to determine the cause of their abdominal distress, and these operations may

have added to the difficulty of subsequent operations and to the increase of morbidity. Long-term follow-up of this group of 20 surgically treated patients revealed that 16 patients were much improved or completely asymptomatic, and that four patients remained essentially the same or had experienced serious postgastrectomy complications. These complications included recurrent ulceration, this time at the site of the gastrojejunal anastomosis, and gastrocolic fistula. One of the patients who had undergone gastroenterostomy and had a subsequent anastomotic ulcer underwent gastric resection of the Billroth I type. Postoperatively, an obstruction unresponsive to conservative management became evident and necessitated a secondary operation; the obstruction was found to be due to cicatricial contraction in the second portion of the duodenum secondary to a postbulbar duodenal ulcer. One patient whose condition was definitely improved had an isolated episode of gastrointestinal bleeding, the exact site of which could not be determined by x-ray examination.

The main concern mentioned in the literature has been the high incidence of complications in this type of ulcer. In the present study the incidence of complications was similar to that of the common type of duodenal ulcer except for gastrointestinal bleeding. An incidence of 38% for hemorrhage is somewhat lower than the rates reported in other series. The roentgenologist's increased attention to the postbulbar portion of the duodenum may result in an increase in the number of uncomplicated ulcers diagnosed in this portion.

Summary

In a series of 99 cases of postbulbar duodenal ulcer a history typical of duodenal ulcer was apparent in two thirds of the patients. An atypical, though suggestive, history of ulcer was noted in 16%. Pain was absent in 16%. The incidence of complications of postbulbar duodenal ulcer was essentially the same as that for the more common type of duodenal ulcer, except that there was a twofold increase in the incidence of bleeding.

Summario in Interlingua

Un ulcere duodenal postbulbar es un ulcere situate in le duodeno distal al bulba duodenal. Minus que 150 tal ulceres ha essite reportate in le litteratura de lingua anglese. Le apparente raritate de iste typo de ulcere ha resultate—in le litteratura—in multe discordo e confusion relative a su incidentia, symptomatologia, e complicationes.

Un diagnose roentgenographic de ulcere duodenal postbulbar esseva facite in 99 patientes del Clinica Mayo in le periodo del 25 annos completate in 1956. Le serie includeva 86 homines e 13 feminas. Dolores esseva le symptoma principal in 83 patientes. Le remanente 16 habeva nulle dolor. Le dolores e le historia clinic esseva considerate como typic in 67 patientes e como possedente fortia suggestive pro le diagnose de ulcere duodenal in 16 patientes additional. Le examine physic esseva sin valor pro le establimento del diagnose. Le studio laboratorial revelava plus que 50 unitates clinic de libere acido hydrochloric in un medietate del casos pro que iste determination esseva effectuate. Minus que 20 unitates esseva trovate in solmente 5% del casos.

Ben que le diagnose esseva facite roentgenographicamente in le totalitate del casos, un tertio requireva duo o plure examines ante que le diagnose esseva absolute.

Complicationes del ulceres duodenal postbulbar non differe in qualitate ab illos del ulceres duodenal usual, sed in le casos postbulbar le complicationes occurre plus frequentemente. Le hic-presentate serie includeva 38 casos de sanguination gastrointestinal, 14 casos de obstruction gastroduodenal, e un caso de perforation acute. Le augmentate incidentia de complicationes resultava totalmente ab plus numerose hemorrhagias.

Le tractamento medical esseva satisfactori in circa un medietate del patientes in qui illo esseva usate. Infelicemente, in multe casos le diagnose esseva establite solmente post que serie complicationes habeva occurrite e requireva un therapia chirurgic. Vinti del patientes requireva interventiones chirurgic. In 15, partial resectiones gastric esseva effectuate. Cinque esseva subjicite a gastroenterostomia.

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THE EFFICACY OF MEDICAL CRITERIA IN DIFFERENTIATING BENIGN FROM MALIGNANT GASTRIC ULCERS *

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Any physician undertaking to treat gastric ulcer patients is faced with a dilemma when he refers to recent medical reports for guidance. Many authors [1-10] advise immediate surgery because of a considerable incidence of unsuspected carcinomas in benign-appearing ulcers. Others [11-17] advise against immediate surgery on the grounds that most gastric ulcers are benign, and complete symptomatic and radiologic response to medical therapy is likely to exclude a malignancy. In 1929 Jordan [18] described a series of medical criteria, involving a trial of therapy, to differentiate benign from malignant gastric ulcers. A similar method of therapeutic trial has been employed at the Veterans Administration Hospital, Cleveland, and the present follow-up study was done in an effort to evaluate the efficacy of this technic.

Case Material and Method of Study

The 135 patients in this group include all those in whom the final diagnosis of benign gastric ulcer was made following a period of hospitalization. They had been seen originally from 1946 through 1953. The series consisted of 134 men and one woman.

Ulcers were located in the body of the stomach in 47 cases and in the antrum in 90 cases, a total of 137 ulcers in 135 patients. Twenty-seven antral ulcers and 29 ulcers of the body of the stomach were associated with normal duodenal bulbs, while a deformed or ulcer-containing bulb was found associated with 63 antral ulcers and 18 ulcers of the body (table 1). Any-

Table 1

Radiologic Findings

Location of Ulcer	Normal Duodenum	Deformed Duodenum	Total
Antrum	27	63	90
Body	29	18	47
Total	56	81	137*

* Two patients had both antral and body ulcers.

* From the Symposium on Gastroduodenal Ulcer, presented at the Thirty-eighth Annual Session of The American College of Physicians, Boston, Massachusetts, April 11, 1957.

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TABLE 2

Age of Patients When First Seen

	Number	Per Cent
Under 20	1	0.7
20–29	15	11.1
30–39	34	25.2
40–49	19	14.1
50–59	43	31.9
60–69	18	13.3
70–79	5	3.7
Total	135	100.0

one with an ulcer which appeared radiologically malignant or which was located on the greater curve was excluded from this series.

Table 2 shows the ages of these patients when first seen. Two peaks in the fourth and sixth decades probably represent the artificial selection which two World Wars have imposed on this veteran population. These peaks are leveled off somewhat in table 3, where patients are classified according to age at onset of ulcer symptoms.

The final diagnosis of benign gastric ulcer was made on the basis of the following criteria:

1. Benign appearance of the ulcer on x-ray or gastroscopy.
2. Presence of free acid on gastric analysis.
3. Complete relief of symptoms on treatment.
4. Complete radiologic healing of the ulcer crater.

With the exception of requiring free acid, these criteria are similar to those outlined by Jordan. She also felt that stools should be negative for occult blood before the diagnosis of benign gastric ulcer was made. This was not routinely tested in the present series.

In certain instances in which the ulcer had decreased in size on treatment but had not healed completely prior to discharge from the hospital, a provisional diagnosis of benign gastric ulcer was made. These patients were advised to return to the hospital or to their private physicians at regular intervals until complete healing had occurred.

Beginning in January, 1954, an effort was made to get into contact with all patients in this study. They were requested to return to the hospital for

TABLE 3

Age of Patients at Onset of Symptoms

	Number	Per Cent
Under 20	4	2.9
20–29	40	29.6
30–39	36	26.7
40–49	21	15.6
50–59	25	18.5
60–69	8	6.0
70–79	1	0.7
Total	135	100.0

follow-up interview and gastrointestinal series. Those who were unable to come to Cleveland because of the distance involved or physical disability were asked to complete a questionnaire. Patients living near another Veterans Administration facility were asked to report there for similar studies. Causes of death were ascertained through reference to Veterans Administration files, death certificates, autopsy protocols or statements from attending physicians.

Results

Adequate follow-up data were obtained in 130 patients (96.4%). Eighty-six patients returned for interview and repeat radiologic studies, while 20 patients replied to the questionnaire. Twenty-four persons had died from all causes. Two (1.5% of those followed) had died from carcinoma of the stomach, four from perforated peptic ulcer, one from serum hepatitis following gastric resection, and 17 from causes other than gastric ulcer or gastric cancer (table 4). The median follow-up period was 46 months.

Table 4

Causes of Death

Cancer of the stomach	2
Perforated ulcer	2
Perforated ulcer with hemorrhage	2
Serum hepatitis*	1
Myocardial infarction	11
Other carcinoma	2
Other†	4
Total	24

* Occurred following blood transfusion during gastric resection.

† Includes one death each from cirrhosis of the liver, cerebrovascular accident, tuberculosis, trauma.

During the years in which this series of patients was accumulated, 27 other patients had a gastric resection performed at this hospital because of nonhealing of a gastric ulcer following a trial of medical therapy. In one of these patients the ulcer was malignant. He had had typical benign ulcer symptoms for three years, and a previous diagnosis elsewhere of peptic ulcer. His lesion was considered benign on initial radiologic study, but a second gastrointestinal series after a period of medical therapy led to suspicions of malignancy. Six further patients, operated upon because of an initial clinical or radiologic impression of possible cancer, were found to have benign ulcers. Gastric resections were performed on nine more patients because of recurrent gastric ulcer within a six-month period. All of these were benign.

Two gastric ulcer patients not included in this series were operated upon because a new ulcer crater appeared during the course of therapy. One of these proved to be malignant. During the eight years in which this group of patients was collected, surgery confirmed the initial clinical impression of cancer of the stomach in 61 other patients at this hospital.

The case histories of the two patients in this series who proved to have cancer of the stomach are summarized below:

Case Reports

Case 1. A 44 year old man entered the hospital on March 21, 1952. During the previous three weeks he had experienced frequent episodes of epigastric pain, relieved by vomiting. Seven years earlier he had noted similar pain, associated with the passage of tarry stools, and had consulted a physician, who informed him that he had a peptic ulcer. Subsequent recurrences of pain lasting from two to four weeks had appeared twice a year.

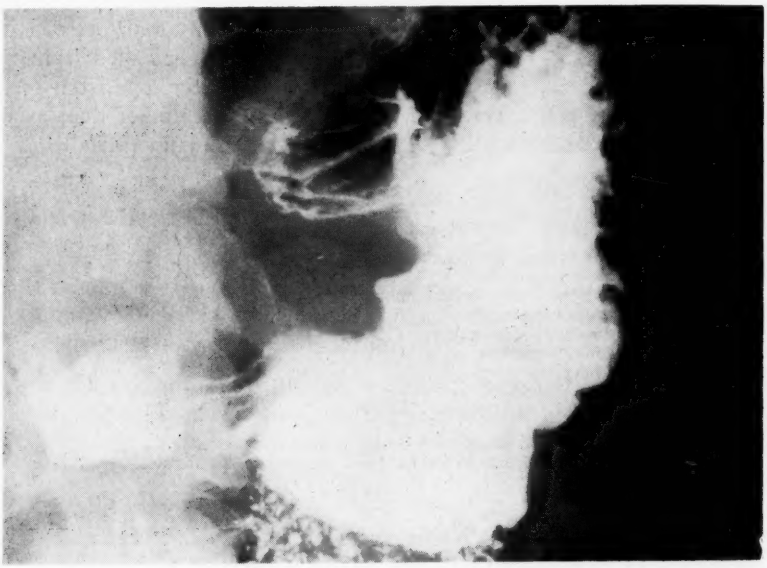

Fig. 1. Upper gastrointestinal x-ray in case 1, showing an apparently benign gastric ulcer. Fifteen months later, an obstructing carcinoma was found at the same site.

Physical examination was not remarkable. Free acid was present on gastric analysis. An upper gastrointestinal series (figure 1) showed a mid-lesser-curve ulcer of the stomach, interpreted as probably benign.

Under treatment, all symptoms disappeared within the first week of hospitalization. He was discharged on the thirty-third hospital day at his own request after he had assured the ward physician that he would return to his private practitioner for a follow-up gastrointestinal series. He neglected to do this, but remained asymptomatic for the next 14 months. After this period, epigastric pain and vomiting recurred and he was re-admitted to the hospital. Radiologic studies showed complete pyloric obstruction, probably due to neoplasm. At surgery, a poorly differentiated adenocarcinoma of the stomach was found, involving the site of the previous ulcer crater.

Case 2. A 74 year old veteran of the Spanish-American War was admitted on September 18, 1951, complaining of shortness of breath and ankle swelling. Despite the fact that he was confused and debilitated, he was able to give a history of past and

recent indigestion. An upper gastrointestinal series demonstrated a mid-lesser-curve ulcer (figure 2), which was considered to be possibly malignant because of its ragged appearance.

The patient's clinical condition was poor, due to congestive heart failure and a recent cerebrovascular accident. On this basis it was felt that exploratory surgery was inadvisable and that his ulcer should be treated medically, despite the doubt as to its benignity. He died two months later at his home. No autopsy was performed, but his physician listed cancer of the stomach as the probable cause of death. The patient is included in this series because his discharge diagnosis was gastric ulcer.

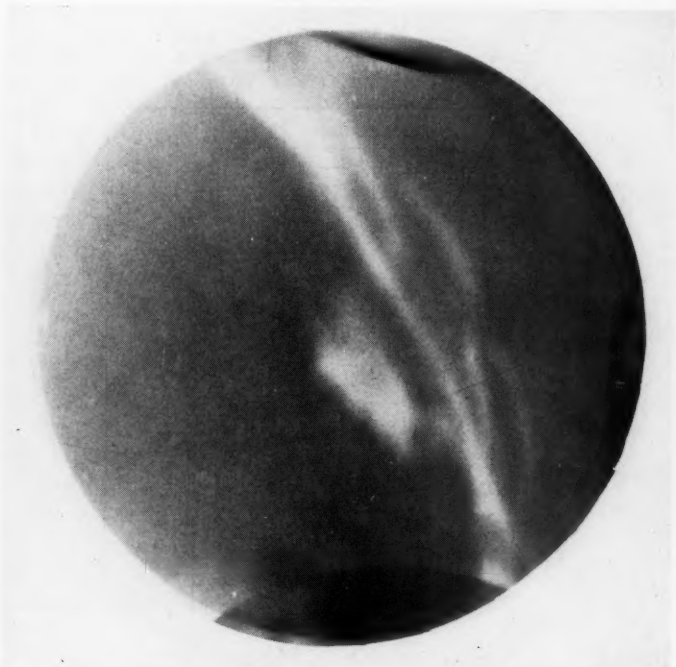

FIG. 2. X-ray in case 2, showing a gastric ulcer of doubtful benignity. This patient was not operated upon because of severe cardiac disease.

DISCUSSION

The experience presented in this study of 135 patients with gastric ulcer indicates that medical criteria can be effective in differentiating benign from malignant lesions. The incidence of misdiagnosed malignant ulcers in the present series was 1.5%. Recent medical reports (table 5) reveal an incidence of cancer ranging from 28.6 to 0% in apparently benign gastric ulcer. These percentage differences appear to depend on the criteria used in the diagnosis of benign gastric ulcer. It is also likely that the experience and proficiency of the individual radiologist are variable factors.

In the present series, if the ulcer appeared benign after careful fluoroscopic and radiologic study, if the stomach secreted hydrochloric acid, and if after treatment in hospital the symptoms were relieved and the ulcer healed, the final diagnosis of benign gastric ulcer was made. In other studies the diagnosis was often a provisional one, based only on initial examination. In some surgical studies [1-4] no prior medical treatment was used to test the diagnosis before gastrectomy, and the incidence of carcinoma was usually high.

TABLE 5

Incidence of Cancer in Apparently Benign Gastric Ulcers

Author	Patients Treated		Follow-Up			Cancer in Series	
	Medically	Surgically	Type	Years	Per Cent	Number	Per Cent
Hayes (1955)	—	196	—	—	—	56	28.6
Marshall (1948)	—	131	—	—	—	26	19.8
Banks (1953)	48	—	Q, I	—	—	8	16.7
Smith (1953)	—	578	—	—	—	81	14.0
Lampert (1950)	—	550	—	—	—	73	13.5
Krarup (1946)	57	—	Q	5–15	94	7	12.3
Sawyers (1956)	186*		—	2–10	92	22	11.8
Johnsson (1950)	219	—	I	7.5	—	25	11.4
Ravdin (1953)	—	99	—	—	—	11	11.0
Cain (1952)	336	—	Q	—	95	33	9.8
Hayes (1955)	231	—	—	5	82	17	7.4
Welch (1949)	512*		—	—	—	34	6.6
Malmros (1949)	192	—	Q	7–10	99	12	6.2
Vaughan (1952)	128	93	I	—	95	13	5.9
Levin (1954)	121	—	Q, I	1–17	—	7	5.7
Flood (1950)	101	—	I	5.6	—	5	5.0
Fierst (1955)	70	—	—	2–8	—	3	4.3
Bille (1949)	908	—	Q, I	1	—	26	2.9
Martin (1949)	251	—	Q, I	10	96	6	2.4
Gott (1954)	88	—	I	5	97	2	2.3
Smith (1953)	422	—	—	5	94	7	1.6
Swynnerton (1953)†	262	—	Q, I	5–12	95	4	1.5
Swynnerton (1953)†	—	254	Q, I	5–12	97	4	1.5
Dworken (1957)	135	—	Q, I	4	97	2	1.5
Brown (1953)	715*		—	—	—	8	1.1
Browne (1954)	200	—	—	—	—	2	1.0
Barsby (1951)	56	—	—	—	—	0	0
Geddes (1956)	70	—	I	4	98	0	0

* Combined medical and surgical series.
† Selected series of chronic ulcer patients.
Q—Follow-up by questionnaire.
I—Follow-up by interview.

In other reports,[6-9] medical therapy was attempted without insistence on radiologic healing for evidence of benignity. Again the incidence of cancer was high.

Still other authors [10-11] have followed benign-appearing gastric ulcers to healing. However, in their final incidence figures for unsuspected cancer, they have included ulcers operated upon for nonhealing. These were often malignant ulcers which had been detected by the therapeutic process itself.

When these cases are excluded from consideration, the incidence of cancer becomes similar to that reported in the present series. The low incidence of cancer in healed ulcers as reported by others is shown in table 6.

The two cases of cancer encountered in this study illustrate the difficulties which may appear in managing gastric ulcer patients. Even though healing was not demonstrated in either case, they are included in the series because the patients were discharged with a benign diagnosis.

The first patient had a seven-year history of very frequent ulcer recurrences, free gastric acidity, and a lesion which appeared benign on radiologic study, together with a good response to medical treatment. This reaffirms the fact that a benign ulcer history and appearance do not rule out a malignant lesion. The failure to obtain a subsequent gastrointestinal series in the hospital, and the patient's negligence, despite advice, to see his physician upon discharge from the hospital, probably account for the diagnostic error in this case.

In the second patient, ideal management was impossible because of complicating illnesses. In reality, he should not have been diagnosed as benign

TABLE 6

Malignant Ulcers Which Have Shown Complete Radiologic Healing

Author	Number	Per Cent of Series
Flood (1950)	4	4.0
Sawyers (1956)	5	2.7
Gott (1954)	2	2.3
Swynnerton (1953)	3	1.1
Welch (1949)	2	0.4
Smith (1953)	4	0.4
Bille (1949)	2	0.2
Barsby (1951)	0	0
Dworken (1957)	0	0

because there was no practical way to submit his ulcer to the strict management program outlined above.

These cases illustrate the fact that following a patient with a gastric ulcer is often a complicated clinical problem. It is probably more difficult in a private or clinic practice than it is in a population consisting solely of veterans. Persons in the former group may not wish to return to the physician making the initial diagnosis, or may object to the expense of repeated gastrointestinal studies. They may seek advice elsewhere and so delay definitive management of a malignant disease beyond the time of possible surgical cure.

Veterans are often required by financial considerations to continue receiving medical attention from one agency, so that failure to heal a gastric ulcer can be noted promptly and the need for surgery appreciated earlier. This factor may also account for the relatively low incidence of overlooked cases of carcinoma found in this and other studies [12-13] on veterans. Whatever his type of practice, any physician undertaking to manage a patient with

gastric ulcer by medical means assumes a large responsibility. It is discharged only when the ulcer is found to have healed completely on follow-up study.

The present data also indicate that two previously unsuspected malignant ulcers were detected by means of a medical therapeutic program. In one case the ulcer did not heal during the treatment period, and in the second case a new ulceration appeared distal to the original lesion. Although many more benign ulcers did not heal and were accordingly operated upon, it is important to recognize the potentially grave significance of an intractable ulceration.

This group of gastric ulcer patients differs from others in that antral ulcers were noted in 66% of the cases. The usual incidence is around 30%.[28] This would not explain the low incidence of carcinoma, since malignant ulcers in the antrum are common. A high incidence (59%) of duodenal deformity was also found in this series, whereas the usual occurrence is 5 to 14%.[28] Such duodenal deformities do not preclude malignancy in

TABLE 7

Late Appearance of Carcinoma of the Stomach

Author	Years after Ulcer Healing			Per Cent of Series
	5–10	10–20	Over 20	
Flood (1950)	2	1	—	3.0
Cain (1952)	11	—	—	2.7
Smith (1953)	2	—	1	0.7
Swynnerton (1953)	2	—	—	0.4
Sawyers (1956)	—	1	—	0.5

an associated gastric ulcer, and have been reported to appear in as many as 29% of patients with malignant gastric ulcers.[29]

It has been suggested elsewhere that the tendency toward carcinoma of the stomach may be increased in patients who have had a previous gastric ulcer, and a few cases of late-appearing carcinomas have been reported (table 7). The present investigation has not been carried on for a sufficiently long period of time to yield any information on this important subject.

SUMMARY

One hundred thirty of a total of 135 patients who had been given a final diagnosis of benign gastric ulcer were followed for a median period of 46 months. Two of these patients were found to have had a carcinoma of the stomach. In each instance, failure to obtain radiologic evidence of ulcer healing prior to discharge from the hospital was the probable cause of misdiagnosis. In addition, two other patients who had been thought to have benign ulcers at the start of therapy were eventually operated upon because

of nonhealing and were found to have malignant lesions. The difficulties of following a patient to complete ulcer healing are discussed. An effort is made to review recent medical reports on this subject and to explain the great variation in the incidence of carcinoma encountered in apparently benign gastric ulcers. This seems to be due primarily to different interpretations of the term "apparently benign," as well as to various ways of handling the statistical data. The present findings indicate that strict medical criteria can successfully differentiate benign from malignant lesions.

SUMMARIO IN INTERLINGUA

Cento trenta-cinque patientes esseva dimittite ab iste hospital inter 1946 e le fin de 1953 con diagnoses final de benigne ulceres gastric. Le diagnose esseva basate super le sequente criterios: Apparentia benigne del ulcere in le prime studio radiologic, presentia de acido libere in le analyse gastric, alleviamento complete del symptomas sub le effecto del therapia, e complete sanation del crateres ulcerose al tempore del repetition del studio radiologic. Omne altere patientes con ulcere gastric esseva excludite ab iste serie. A partir de 1954, iste patientes esseva instruite a retornar pro studios consecutori visante a probar le efficacia del methodos medical in le differentiation de benigne ab maligne ulceres gastric. Informationes esseva de facto obtenite pro 130 patientes (i.e. 97% del serie total). Le periodo median del observation consecutori esseva 46 menses. Esseva trovate que duo del patientes (i.e. 1,5%) habeva habite carcinoma gastric. In ambe iste casos, le re-evaluation del dossier hospitalari revelava que le supra-listate criterios non habeva essite observate adequatemente. In le prime caso, le prova radiologic del sanation del ulcere non habeva essite obtenite, durante que le secunde patiente habeva essite placiate sub le regime medical solmente a causa del facto que ille esseva considerate como troppo debile in consequentia de un altere morbo pro indurar chirurgia exploratori. In le curso del annos del presente studio, duo altere patientes esseva discoperite qui habeva carcinoma gastric a causa de incomplete sanation del ulceres per le therapia medical. In ambe iste casos, le lesiones habeva originalmente essite considerate como benigne. Es sublineate le difficultates del correcte tractamento medical de ulceres gastric a apparentia benigne. Es exprimite le opinion que le meticulose observation del criterios medical es efficace in le differentiation de benigne e maligne ulceres gastric.

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GENERALIZED TETANUS: ANALYSIS OF 202 CASES *

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SINCE the discovery of the antibiotics there has been a spectacular advance in the ability to control diseases of bacterial origin that in the past had a high mortality rate.

Much has been learned through the years about the etiology,[1, 2] clinical picture, pathologic physiology [2-6] and treatment [4, 7-10] of tetanus. Although the chances of survival in this disease have increased in recent years, it is still one of the diseases of bacterial origin with a very high mortality rate.

It is the purpose of this paper to evaluate our clinical experience with 202 cases of generalized tetanus in order to stimulate further interest in the study of the control and treatment of this dreadful disease.

CLINICAL OBSERVATIONS

This report is based on a study of 202 adult patients admitted to the Medical Service of the Fajardo District Hospital with the diagnosis of tetanus from October, 1940, to November, 1955.

Age: The youngest patient was 12 years old and the oldest was 84. The relative frequency of the disease according to age and the relationship of age to mortality rate are illustrated in table 1.

Sex: The disease was three times as frequent in the male as in the female. There were 150 males and 52 females.

Race: Ninety-three patients were colored and 109 were white. No racial predisposition was encountered considering the ratio of white to colored population admitted to our hospital.

Occupation: Seventy-two patients were laborers, 47 were housewives and 35 were students. The remaining 48 patients were engaged in various occupations.

TABLE 1

Age Distribution and Mortality Rates in 202 Cases of Tetanus

Age in Years	Cases	Deaths
12–19	75	14
20–29	39	12
30–39	33	14
40–49	18	7
50–59	12	6
60–69	17	8
70+	8	5

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TABLE 2

Portal of Entry and Mortality Rates in 202 Cases of Tetanus

Portal of Entry	Cases	Deaths	Mortality Rate
Upper extremity	35	9	25.7%
Lower extremity	103	35	33.9%
Head and neck	21	8	38.4%
Trunk and genitalia	3	2	
Interior of abdomen	5	2	
Multiple sites	4	2	
Unknown	31	8	25.8%

Site of Injury: Table 2 demonstrates the portal of entry and its relationship to mortality. The lower extremities were most frequently the site of entry. No significant difference was found in the mortality rate in a comparison of the cases with the portal of entry in the head and neck with those with the portal of entry in the lower extremities.

TABLE 3

Incubation Period	Cases	Deaths	Mortality Rate
Ten days or less	86	37	43.02%
More than 10 days	41	8	19.59%

Incubation Period: In 127 patients the incubation period was known exactly; in 75 it was not determined. Twenty-seven patients had chronic leg ulcers, 31 an unknown portal of entry, and in 17 the site but not the date of injury was known.

Table 3 illustrates the relationship of the incubation period to death. Those patients with a shorter incubation period had a higher mortality rate.

TABLE 4

Symptoms in 202 Cases of Tetanus

Trismus	171
Convulsions	75
Dysphagia	64
Back pain	59
Stiff abdomen	53
Stiff neck	53
Stiff back	42
Fever	38
Neck pain	33
Sore throat	32
Stiff extremities	27
Chest pain	21
Generalized stiffness	19
Spasms	14
Abdominal pain	14
Profuse sweating	10
Chest oppression	7
Malaise	7
Generalized myalgias	6
Difficult breathing	6

Of the 66 patients who died, 45 had a known incubation period. As shown in the above table, 37 of these 45 cases had an incubation period of 10 days or less, or 82.22% of the total deaths with a known date of entry.

Symptoms: Thirty-three of the patients who died had been brought to the hospital within 24 hours of the onset of the initial symptom.

Table 4 demonstrates the relative frequency of symptoms. Pain in the legs, muscular twitchings, facial paralysis, irritability and anorexia were complaints in a small number of cases. It is apparent from table 4 that the main symptomatology in tetanus is referable to the neuromuscular system.

Signs: Table 5 illustrates the relative incidence of different physical signs. It will be noted that the striking objective findings are also the result of changes secondary to increased activity of the neuromuscular system.

One hundred seventy-three patients had fever. In 43 the temperature

TABLE 5

Physical Signs in 202 Cases of Tetanus

Trismus	196
Fever	173
Abdominal rigidity	168
Hyperactive deep reflexes	137
Nuchal rigidity	137
Convulsions	118
Opisthotonos	95
Tachycardia	74
Risus sardonicus	60
Stiff extremities	55
Profuse diaphoresis	25
Facial paralysis	11
Hypoactive reflexes	8

was above 39.5° C. Fifteen of the latter recovered. Only two deaths occurred in the 29 afebrile patients.

Convulsions occurred in 118 patients, of whom 52 died. Of 84 patients without convulsive episodes, only 14 died.

Laboratory: Cultures for *Clostridium tetani* were not performed, but the clinical picture was typical in all instances. As bacteriologic confirmation was not obtained, all doubtful cases were eliminated from this study.

A leukocyte count over 10,000 per cu. mm.[3] was obtained in 35.8% of the cases. Slight to well marked albuminuria was found in 62 instances.

Hospital Stay: The length of hospitalization ranged from five to 56 days in the 136 cases that survived. The average hospital stay was 22.9 days. Fifty-two of the 66 patients who died lived less than seven days after admission to the hospital; 25 of these lived less than 36 hours after admission.

Prophylaxis and Immunity: Six of the patients had received a prophylactic dose of 1,500 units of tetanus antitoxin the day of injury; five survived.

Recurrence of the disease occurred in five patients. The periods between successive attacks were five months, 19 months, five years, 10 years and 16 years. The portal of entry in four of the cases was a chronic leg ulcer. The

only death was the patient with recurrence of the disease five months after the original attack.

Treatment: The patients were admitted to a specially selected, quiet dark room. All received tetanus antitoxin after skin testing. It was administered in initial doses of 20,000 to 100,000 units intramuscularly, and 20,000 to 100,000 units intravenously, diluted in 300 to 1,000 c.c. of saline or 5% glucose solution. Further doses, ranging from 20,000 to 80,000 units per day, in single or divided doses, were given for a period of from three to 12 days.

The best results were obtained in those cases that received 30,000 to 60,000 units intramuscularly and 40,000 to 60,000 units intravenously as the initial dose, followed by 10,000 to 20,000 units twice a day for a period of from three to five days.

Debridement of the site of injury after local injection of 10,000 to 20,000 units of tetanus antitoxin was performed in 60 instances. In the remaining cases, the site of entrance was carefully cleaned and oxidizing agents were applied locally. No significant difference in the mortality rate in these two groups was noted.

TABLE 6

Penicillin and Mortality Rate

	Cases	Deaths	Mortality Rate
No penicillin	46	16	34.9%
Crystalline penicillin	74	27	36.5%
Procaine penicillin	84	23	28.0%

All patients received parenteral phenobarbital sodium in doses of 1 to 5 gr. every three to six hours, according to the severity of the restlessness, irritability and convulsions. The usual dosage required was 2 to 3 gr. every four to six hours. The largest total dose given in 24 hours was 30 gr. When the convulsions could not be controlled with phenobarbital sodium, other drugs were used: paraldehyde per rectum in six cases, Avertin (tribromoethanol) in 29, and chloral hydrate in 14.

In some cases the trismus and dysphagia interfered with adequate oral feeding and hydration. These patients were given from 2,000 to 3,000 c.c. of intravenous fluids daily until they were able to take food and liquids by mouth.

Forty-six of the patients in this series were treated prior to the penicillin era. Table 6 illustrates the influence of the different types of penicillin on the survival rate. The administration of crystalline penicillin consisted of an initial dose of 30,000 to 100,000 units intravenously or intramuscularly, followed by an intramuscular dose of 15,000 to 50,000 units every three hours for from three to 12 days.

Procaine penicillin was administered in doses of 300,000 to 400,000 units daily or twice a day for from one week to one month in 63 cases. In 19

cases a dosage of 800,000 to 1,000,000 units twice a day was given. Seven of the 19 died.

Tracheotomy was performed in only 11 of the 202 cases; eight of the 11 died.

Deaths: Sixty-six of the 202 patients died, an over-all mortality rate of 32.67%. The apparent causes of death are shown in table 7. The most frequent cause was respiratory failure. This was precipitated either by paralysis of the muscles of respiration [6] or by damage to the respiratory center.[11]

The picture of progressive deterioration, fever, tachycardia and clouding of the sensorium, followed by stupor, profuse diaphoresis, generalized relaxation and death, is attributed to the toxic state of the disease. This accounted for death in 15 patients, and was a contributing factor in another 10. Pneumonia and laryngeal spasm occurred in seven cases.

TABLE 7

Causes of Death in 66 Patients of Tetanus

Respiratory failure	20
Toxemia	15
Laryngeal spasm	5
Toxemia and respiratory failure	5
Sustained convulsions	4
Toxemia and pneumonia	4
Pneumonia	3
Toxemia and laryngeal spasm	1
Laryngospasm and respiratory paralysis	1
Pulmonary edema	1
Undetermined	7

DISCUSSION

Tetanus is an infectious disease of bacterial origin caused by *Clostridium tetani.* Due to its striking clinical picture [12] and the difficulties in isolating the offending bacillus,[13] identification of the Clostridium is not required for confirmation of the disease. The diagnosis can usually be established by a history of recent injury, followed by trismus, dysphagia, nuchal, abdominal or generalized rigidity, convulsions and hyperactive deep tendon reflexes.

The symptomatology as well as the physical signs of the disease is primarily a manifestation of involvement of the neuromuscular system. This is probably due to the effect of the toxin produced by the tetanus bacillus at the site of the original lesion which is distributed by the blood stream and lymphatics to the nervous system, with or without the production of a secondary toxic substance.[4-6, 14, 15]

Although the disease may occur at any age, we have presented only patients over 12 years of age. In the adult, age has some prognostic value, as the mortality rate seems to increase with advancing years.

A higher incidence of tetanus among laborers and school children was found, the probable explanation being their frequent exposure to injury and

closer contact with soil and dust, where the organism usually exists.[1, 16, 17] The relative predominance of the disease in the male sex may be explained in part by the above reasons.

Contradictory reports in regard to the prognostic value of the site of entrance have appeared in the literature.[8, 11, 18] In our cases the site of entry had no apparent influence upon the severity of the disease or the chance for survival. This is explained by the fact that the toxin is carried to the central nervous system by the blood and lymphatics [14, 15] and not by the motor nerves, as was originally postulated.[3] However, the incubation period apparently has a prognostic importance. The mortality rate of the patients with an incubation period of 10 days or less was at least twice that of those with a longer incubation period. This agrees with the generally accepted assumption that a shorter incubation period is associated with a lower survival rate.[8, 9, 18]

A high mortality rate was encountered in those patients brought to the hospital within 24 hours of the onset of the initial symptom. It seems as though patients with a severer type of disease seek medical care earlier. One may speculate as to whether, in these patients, a larger amount or a more potent toxin was originally liberated at the site of injury, thus producing a more fulminant type of disease.

The onset of convulsions and the presence of fever apparently have some bearing upon the final outcome of the disease. The mortality rate in the patients who had convulsions was two and one-half times that of those who did not. This probably implies that a greater amount or a more powerful toxin had been fixed to the tissues. Most of the cases with a temperature above 39.6° C. died, while 27 of 29 afebrile cases survived. Our findings agree with previous observations that a higher temperature means a poorer prognosis.[19] Although in some patients the fever could be ascribed to respiratory infections, in others it was apparently caused by the overwhelming toxemia of the disease.

Six patients developed the disease despite the prophylactic administration of 1,500 units of tetanus antitoxin the day of the original injury. The failure of this prophylactic dose to prevent the development of tetanus has already been pointed out.[20, 21] It is felt that, to obtain better results, a larger dose should be given.

An episode of the disease does not give permanent immunity. Five cases of recurrent tetanus were found in this series. Until recently only 55 such cases had been reported in the literature.[22, 23] The portal of entry in four of the five cases was chronic leg ulcers. Apparently the spores persist at the ulcerated area, with eventual bacterial growth, liberation of toxin and reappearance of the disease.

Once the disease has developed, every point should be taken into consideration in an attempt to save the patient. He should be placed in a quiet, dark room to prevent irritability and convulsions, which lead to exhaustion

and death. After skin testing, tetanus antitoxin should be administered, in doses of 40,000 to 60,000 units intravenously and 30,000 to 60,000 units intramuscularly, to control the circulating toxin. An additional dose of 10,000 to 20,000 units twice a day for from three to five days should be given.

Sedative agents should be administered in an attempt to control the prolonged laryngeal spasms and tetanic convulsions that lead to severe exhaustion. Usually phenobarbital sodium, in doses of 2 to 3 gr. every four to six hours, is adequate. Chloral hydrate, paraldehyde and Avertin rectally may be of great help in the severe cases. The amount of sedation to be given should be carefully controlled, as overdosage can precipitate depression of the respiratory center. An ideal dose is one that controls convulsions and spasms without affecting the vital centers. In some cases it is necessary to use either mephenesin [24, 25] or succinylcholine [26] to control convulsions.

Adequate hydration should be maintained and caloric requirements met by intravenous alimentation in those cases that cannot have oral feedings because of trismus or dysphagia. Gavage feeding is considered contraindicated, as it predisposes to laryngeal spasm and convulsions. If the urinary output is adequate, potassium chloride should be added to the intravenous fluids to avoid hypokalemia. We had a patient with severe trismus and profuse diaphoresis who developed generalized flaccidity, accompanied by electrocardiographic changes of hypokalemia, after intravenous feeding for eight days. This flaccidity, as well as the electrocardiographic findings, disappeared with the administration of potassium chloride in the intravenous fluids.

Debridement after the local injection of 10,000 to 20,000 units of tetanus antitoxin should be performed whenever possible. Although no significant change in the survival rate in the patients that had debridement was noted in this study or in others,[8] we believe that excision of the site where the toxin is produced should be attempted.

Procaine penicillin, in a dose of 400,000 to 800,000 units daily, should be administered to prevent pulmonary infections. Although lack of effect of the drug on tetanus has been claimed,[27] there is experimental work to support some effect of penicillin upon the bacillus in vivo.[28] In our series the mortality rate was somewhat lower in the cases that received it, though apparently death is inevitable once a fatal dose of toxin has already been fixed to the tissues.

Tracheotomy was performed in only 11 cases. Some authors have emphasized the importance of tracheotomy in tetanus.[29-31] We believe that no definite statement in regard to the use of this procedure in all cases of tetanus can be made, as data are not available from a large enough series to justify any conclusions. However, we feel that tracheotomy should be routinely used in all patients with episodes of laryngeal spasm as the best way available to prevent anoxia and death.

The presence of albuminuria in a good number of cases remains unexplained. The possibility that it may be due in part to the foreign protein introduced in the tetanus antitoxin has been considered.

The length of the survival time apparently gives some idea as to the final outcome of the disease. In our experience, once a patient survives seven days of supervised hospital treatment his chance for recovery is markedly increased.

Our mortality figures compare favorably with many reports in the literature.[9, 12, 32-34] However, they are still very high for a disease of bacterial origin.

The most frequent causes of death were respiratory failure, toxemia, laryngeal spasm and pneumonia. With the help of antibiotics, mortality due to pulmonary infections can conceivably be completely eliminated. Laryngospasm can be controlled in part with sedation and tracheotomy. Respiratory failure and the toxemia of the disease are the chief dangers. Apparently the opportunities for survival once a lethal dose of toxin has been fixed to the tissues are practically nil. Our best therapeutic weapon is tetanus antitoxin, but it is not effective upon the already fixed toxin. Further knowledge about control and treatment of this disease is needed.

Summary

1. Two hundred and two cases of generalized tetanus have been analyzed. The disease occurs more frequently in the male sex, in laborers and in school children. The signs and symptoms are those of involvement of the neuromuscular system.

2. Clinical observations of some prognostic significance have been presented. A short incubation period, convulsions, high fever and old age usually mean a poorer prognosis. The portal of entry apparently did not influence the mortality rate.

3. An attack of the disease does not give permanent immunity. Fifteen hundred units of tetanus antitoxin are not an effective prophylactic dose.

4. Treatment has been discussed. All patients should have local debridement, tetanus antitoxin, sedatives and penicillin. All patients with laryngeal spasms should have a tracheotomy. If the patient survives a week of supervised hospital treatment the chance for recovery is greatly increased.

5. The most common causes of death are respiratory failure, toxemia, laryngeal spasm and pulmonary infections. Further knowledge about control and treatment of this disease is needed.

Summario in Interlingua

Es presentate un analyse de 202 patientes adulte con tetano generalisate. Le morbo esseva incontrate le plus frequentemente in individuos de sexo mascule e de racia blanc.

Le gravamines principal concerneva affectiones neuromuscular resultante in trismo, convulsiones, dysphagia, e rigiditate muscular. Le principal constatationes in le examine physic esseva trismo, febre, rigiditate abdominal e nuchal, hyperactive reflexos de tendine profunde, convulsiones, e opisthotonos.

Le mortalitate esseva augmentate in le presentia de plus breve periodos de incubation, convulsiones, alte grados de febre, e etate avantiate. Esseva notate nulle correlation apparente inter porta de entrata e superviventia.

Le administration prophylactic de 1.500 unitates de antitoxina de tetano effectuate le die mesme del vulneration original non serviva a prevenir le morbo in sex patientes. Cinque del patientes disveloppava tetano recurrente. Quatro de istes habeva ulceres chronic al gambas como porta de entrata.

Le therapia debe esser initiate si tosto que le morbo es recognoscite. Un calme ambiente a illumination reducite es a preferer. Debridement (in tanto que possibile), sedativos, e penicillina es indicate. Post tests cutanee, antitoxina de tetano debe esser administrate intravenosemente in doses de 40.000 a 60.000 unitates. Al mesme tempore, 30.000 a 60.000 unitates debe esser administrate intramuscularmente. Doses additional de 10.000 a 20.000 unitates debe esser administrate duo vices per die durante tres a cinque dies. Adequate grados de hydratation intravenose debe esser mantenite si le presentia de trismo resulta in difficultates de alimentation oral. Tracheotomia debe esser effectuate in patientes con spasmo laryngee.

Sexanta-sex del patientes moriva, i.e., le mortalitate amontava a 32,6%. Le plus commun causas de morte esseva disfallimento respiratori, toxemia, spasmo laryngee, e infectiones pulmonar.

Informationes additional in re le subjugation e le tractamento de iste morbo es un desiderato urgente.

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EXPERIENCE WITH THE ANTICOAGULANT, MARCUMAR*

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Anticoagulant therapy is becoming increasingly important in the prevention and treatment of thrombo-embolic disease. Various investigators, in a search for an "ideal anticoagulant," have expressed preferences for one or the other of several drugs of this type which are available commercially or experimentally. Recently many investigators have favored phenindione (Hedulin) as the "anticoagulant of choice." [1]

Among the anticoagulant drugs employed in our clinic since 1943 were bishydroxycoumarin (Dicumarol), cyclocumarol (Cumopyran), ethyl biscoumacetate (Tromexan ethyl acetate), phenindione (Hedulin), diphenadione (Dipaxin) and, more recently, phenprocoumon (Marcumar).† We were greatly impressed with the superiority of phenprocoumon with respect to greater predictability of results and better maintenance of prothrombin levels as compared with the other anticoagulants studied, and therefore wish to present our findings and observations.

Marcumar (3-(1 [1]-phenyl-propyl)4-hydroxy-coumarin) was described as early as 1953 by Koller and Jakob [2] and others. A clinical report on the satisfactory treatment of 100 cases was given by these authors. In July and November, 1954, Wright et al.[3, 4] studied the action of the drug on experimental animals and clinically on a number of patients. The pharmacologic action of the drug was defined by these writers later in the same year as

> "depressing both the proconvertin and prothrombin in the plasma. After oral or intravenous administration of Marcumar to rabbits, proconvertin is the first factor affected. The decrease of this factor can be detected usually within 12 hours after administration. The undilute and dilute prothrombin complex times, however, do not show any change before 18 hours. The peaks of the proconvertin time, and undilute and dilute complex times occur simultaneously after 48 hours. Maximal decrease in prothrombin is observed between 48 and 72 hours. Between the peak of the proconvertin time and the prothrombin time there is a 12 to 24 hour delay. The anticoagulant effect lasts between four and five days when the dosage is equal to or greater than 25 mg. per kilogram.
>
> "It is well known that rabbits on normal diet actively synthesize Vitamin K in the intestines. The duration of anticoagulant activity after oral administration of 2.5 mg. of Marcumar per kilogram is five days when the animal is starved,

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† Marcumar Tablets, 3 mg., were supplied through the courtesy of Dr. Leo A. Pirk of Hoffmann-La Roche Inc., Nutley, New Jersey.

but is reduced to three days when the rabbit is on a normal diet. Under the same conditions the anticoagulant activity of Marcumar after intravenous injections of 10 mg. is reduced from four days to one day. These findings suggest the antagonistic effect of Vitamin K_1 on the anticoagulant activity of Marcumar."

These findings have since been corroborated by many investigators, and the very practical applications derived from this early work must be borne in mind in certain types of cases and may well alter dosage schedules.

In a general way one can divide anticoagulants into short-acting drugs such as Hedulin and Tromexan, and those with more prolonged action, such as Dicumarol, Cumopyran and Marcumar.

It is claimed that short-acting drugs such as Hedulin obtain a quick therapeutic blood level, and that rapid rising of the blood prothrombin will occur should its discontinuance be desired. As to the former, it is our experience that therapeutic blood levels may indeed be obtained within 12 to 24 hours in many cases on giving the recommended dosage of 200 mg. However, it became evident to us that, on the recommended initial dose, the blood prothrombin time levels of a fair proportion of patients rose within 36 hours to a level higher than we deem necessary. At this point further dosing is unwise, yet in many cases levels have dropped by the next day to a point of therapeutic inadequacy. In a general way our experience has been that continuation of therapy with the shorter acting anticoagulants tends to perpetuate this "peak-and-valley" type of curve. In the practical therapy of patients, then, the advantage of this "quick therapeutic level" is overshadowed by the more stable levels obtained with such a drug as Marcumar.

In purely prophylactic use such as in *postoperative* and *post partum* cases adequate levels are obtained with Marcumar before the usual time of occurrence of thrombo-embolism is reached. Thrombo-embolic complications rarely occur before the third day after an acute attack of coronary thrombosis, and by this time, adequate therapeutic levels are reached with Marcumar. However, in our opinion any coronary case presenting itself at a later or even unknown date after an original attack calls for the prompt use of heparin. In fact, many conditions requiring immediate anticoagulation will call for the initial use of heparin rather than short-acting anticoagulants.

The rapid disappearance of Hedulin or other short-acting anticoagulants on discontinuing the drug cannot be denied. With the advent of K_1 this advantage is somewhat theoretic, as blood prothrombin levels obtained with the longer acting anticoagulants, such as Marcumar, can in our experience be increased with great celerity if necessary.

In more recent years we have observed in many cases the value of minimal doses of K_1 orally at any stage where the prothrombin depression is somewhat more than that desired. Such minimal doses are often quite adequate to prevent any upswing in the prothrombin time, but there is a very real advantage of not lowering the prothrombin time below the therapeutic level. We find the occasional use of oral K_1 in minimal doses

has worked very well in connection with our use of Marcumar. Despite the usual predictable response from the latter, in certain sensitive cases the oral use of vitamin K_1 has contributed to obtaining much more stable prothrombin curves.

Thus we feel that the shorter acting anticoagulants show no practical advantage over Marcumar, and believe that this latter drug surpasses such other longer acting drugs as Dicumarol and Cumopyran.

Method of Study

Our clinic at the present time averages approximately 800 out-patients and 60 in-patients on anticoagulant therapy. This report comprises a study of 1,568 hospital patients treated with Marcumar from June, 1955 to March, 1956. These patients comprise a series of cases listed under the following headings: Acute coronary thrombosis or insufficiency, acute phlebitis, and post-operative and post-partum prophylactic therapy.

The action of Marcumar in these cases was studied specifically as to (1) rapidity of obtaining a therapeutic level; (2) the stability of the curve, once obtained; (3) the value of certain measures to insure the stability of the curve; (4) the incidence of hemorrhage, and (5) the ability to lower the prothrombin time rapidly should the necessity arise.

In addition, 288 out-patients under long-term therapy for coronary disease and recurrent phlebitis were studied comparing the merits of the three long-acting drugs, Marcumar, Dicumarol and Cumopyran.

In this study prothrombin times were done by the one-stage method of Quick. In the opinion of most workers in this field, "the prothrombin per cent of normal" is seldom used in practical therapy. Moreover, the reporting of prothrombin times in 12.5% dilute plasma gives little additional value in the therapy of patients.

Evaluation of Marcumar in Classified Cases

Acute Myocardial Infarction: Fifty-six consecutive hospital cases were given Marcumar as the anticoagulant. Of this series of patients, as well as of other types of cases reported, a graphic record is given, together with an objective evaluation of therapeutic results. The average length of hospitalization in this group was from three to eight weeks.

In our clinic these "coronary" patients, provided their initial prothrombin time is normal, are given a "loading dose" of 30 mg. of Marcumar on the first day. No dosage is given on the second day. The third and fourth days will be the peaks of action of the initial dosage. With this in mind they are conservatively dosed on the third day, unless they are resistant. Our experience has been that many patients with coronary thrombosis seem to have a hypercoagulability or resistance to therapy which must be overcome. This resistance is usually evident by 36 hours, and dosage is ad-

TABLE 1

	10	20	30	40	50	
E	##########	##########	#########			29 cases
G	#######					7 cases
S	##########	##				12 cases
R	########					8 cases

E—Excellent records of 25 to 35 seconds at all times.
G—Good levels of 20 to 30 seconds at all times.
S—Sensitive. So classified because, while considered excellent on the average through their three- to eight-week therapy, once or twice during their stay levels rose to 40 to 50 or 60 seconds. (The level of one such patient on one occasion rose to 96 seconds.)
R—Resistant. So classified because, on the average, the levels of these patients dropped below 20 seconds once or twice in their four to eight weeks of therapy. (The level of one of the eight cases dropped below 20 seconds repeatedly.) It may be mentioned that, aside from these exceptions, the levels were considered good. There was no incidence of bleeding in this series.

justed accordingly. Thus, if on the third day after the loading dose the blood prothrombin level does not suggest resistance but is approaching the desired levels, a daily dosage of 3 mg. might well be instituted. However, a case showing resistance on the third day could be given 9 or 12 mg. at this point. At all events, when the desired level is reached the maintenance dose must of necessity vary, depending upon whether the case proves to be resistant (or possibly sensitive), and such dosages may well be as low as 3 mg. every other day, on up to 6 mg. daily. Further than this no didactic rule can be given, and, especially in coronary cases in their early stage, daily prothrombin times must guide the dose. We believe that, particularly in coronary cases where clotting has already occurred, one should not make the error of being too conservative in producing prothrombin depressions.

Consequently, the prolonged action of Marcumar seems to us most desirable in these cases. Once a level of 32 to 34 seconds is attained, it can often be maintained without further dosage for from two to four days. With the shorter-acting anticoagulants this is not possible, in our experience. We watch any high prothrombin time under 45 seconds in the early stages of a coronary case without giving any vitamin K_1. Usually there is a slow drop over a period of from four to five days, giving a very satisfactory level.

Acute Phlebitis: Twenty-four consecutive hospital cases were treated with Marcumar. The length of hospitalization was from one to eight weeks.

In such phlebitis cases a very satisfactory level is obtainable. In the foregoing coronary cases, complicating circulatory, kidney or liver disorders often appear and make difficult the establishment of a stable and non-fluctuating prothrombin curve. In our cases of phlebitis we found very few such complications and were able to obtain such "excellent" curves without difficulty. There was no incidence of bleeding in this series.

The dosage management in these cases is similar to that used in coronary cases.

TABLE 2

	10	20	30	40	50	
E	##########	#########				19 cases
G						0 cases
S	#					1 case
R	####*					4 cases

Key—Same as for acute myocardial infarction.

#*—Always resistant—below 20 seconds consistently. Must be considered a failure as far as anticoagulation is concerned (one case).

Postoperative Prophylaxis: We shall first present our experience with the routine prophylactic use of Marcumar in postoperative cases excluding gallbladder, gastric or colon surgery. These latter comprise, in our opinion, a special group which present specific problems therapeutically and which must be handled very carefully. They will be discussed later. The length of hospitalization in postoperative prophylaxis ranged from one to two weeks. A great majority of such cases gave a normal initial prothrombin time, and at present only these cases are included.

TABLE 3

	50	100	150	200	250	300	350	400	
E	######	######	######	######	######	######	#		304 cases
G									0 cases
S	###								29 cases
R2	##								10 cases
R3	#								2 cases
Always R	######	##							52 cases
									397 Total

E—Excellent record (20 to 35 seconds).

G—Good. No cases so classified because in prophylactic anticoagulation we consider 20 to 35 seconds to be fully adequate.

S—Sensitive. So classified because the records are considered satisfactory with certain exceptions: 19 cases showed one episode of between 36 and 50 seconds, nine cases reached on one occasion 50 to 69 seconds, one case rose to 134 seconds.

R2—Resistant. Considered to be a satisfactory record except that each case twice had a level below 20 seconds.

R3—Resistant. Considered to be a satisfactory record except that each case three times had a level below 20 seconds.

Always R—Always resistant. Given usual initial dosage. Always below 20 seconds. (Most of these patients had a short hospital stay of from four to five days.)

The initial loading dosage in this type of case was 24 mg. of Marcumar. In maintenance of a prophylactic level, procedures were mainly the same as those outlined earlier. However, since the therapy here is purely prophylactic, a somewhat conservative prothrombin depression has proved adequate; hence maintenance doses are often, but not necessarily, smaller than in cor-

onary cases. Bleeding occurred three times during anticoagulant therapy in this series of 400 postoperative cases. Bleeding was not severe in any of these cases, and transfusion was not necessary in any case. Two of these cases required vitamin K_1 intravenously. Anticoagulant therapy was discontinued when bleeding occurred.

Postoperative Prophylaxis in Bowel, Stomach or Gall-Bladder Surgery: A total of 91 such cases were treated with Marcumar. The initial prothrombin time averaged 17 to 20 seconds.

TABLE 4

	10	20	30	40	50	60	
E	########	########	########	########	########	#####	56 cases
G							0 cases
S	########						10 cases
R	########	######					18 cases
F	######						7 cases
							91 Total

E—Excellent (18 to 35 seconds).
G—Good. None so classified, because 18 to 35 seconds was considered to be adequate in these cases.
S—40 to 50 seconds once or twice, otherwise good records. (One case rose to 80 seconds.)
R—Always below 20 seconds.
F—Fluctuates.

These patients are extremely difficult to manage. Many authors actually list them among the cases in which anticoagulant therapy is contraindicated. However, in this very type of case the hazard of thrombo-embolism is greater than in the general run of postoperative case. Hence, with extreme caution Marcumar prophylaxis was instituted in 91 cases. It is evident from the chart that in a large percentage it was possible to maintain satisfactory prophylaxis. There was no instance of thrombo-embolism in this series.

Anticoagulant therapy was discontinued in one case because the prothrombin level was 80 seconds; no bleeding occurred. A case of postoperative hemicolectomy developed a hematoma in the abdominal wall while on anticoagulants with a level of 20 seconds. Anticoagulants were discontinued, and no further difficulty occurred. A third patient had a subtotal gastrectomy for chronic gastric ulcer. On the fourth day after institution of anticoagulant therapy the patient began vomiting dark blood and passing tarry stools. The hemoglobin at that time was 69% and the prothrombin time 40 seconds. A pint of whole blood and 25 mg. vitamin K_1 intravenously were given. No further bleeding occurred and anticoagulants were discontinued. Ten days later this patient died and autopsy revealed massive pulmonary embolism.

Postoperative patients with Wangensteen suction present very definite problems in management. It is our experience in such cases that immediate

therapy with even 3 mg. of Marcumar may well send the prothrombin time to a high level. For this reason we have been withholding the drug until after the tube has been removed. At this stage 3 to 6 mg. on alternating days will often attain a therapeutic level. To a somewhat lesser extent care must be used in initiating anticoagulant therapy where there is a tube in the common bile duct. In this group of cases without any drainage tubes post-operatively, an initial dose of 9 mg. usually gives a satisfactory response and can be followed by routine maintenance dosage.

Postpartum Cases Treated with Marcumar: Patients in this group were usually discharged four to five days after delivery, in some cases after only

TABLE 5

	100	200	300	400	500	600	700	800	900	1,000	
E	#####	#####	#####	#####	#####	#####	#####	#			716 cases
G											0 cases
S R 36 hr.	#										17 cases
	#####	####									186 cases
Alw. R	####										81 cases
											1,000 Total

E—Excellent (20 to 35 seconds).
G—None so classified.
36 hr. R—Checked only once after initial dosage and discharged prothrombin time 20 seconds.
Always R—Below 20 seconds prothrombin time during four to five days in hospital. Usually 17 to 19 seconds. (Still possibly had prophylactic value altering Factor VII and prothrombin.)

three days. Blood samples were taken every other day unless the preceding prothrombin time was 30 seconds or over. The initial dosage with a normal prothrombin time on postpartum patients was 24 mg. Marcumar. In such postpartum cases and in certain short-term postoperative cases the action of Marcumar is especially valuable. Its prolonged action on Factor VII and prothrombin, lasting from five to seven days following the initial dosage, maintains adequate prophylaxis against thrombo-embolic complications even after the patient has been discharged from the hospital.

CHANGES IN WEATHER AFFECTING DOSAGE

We feel it important at this point to cite our experience with the effect of anticoagulants given to patients in very hot weather as compared to cooler weather. We have found that, in those exhibiting sensitivity to the drug, an almost consistent percentage will have a hyperresponse in hot weather. Hence, in our clinic, in prophylactic therapy, the standard of dosage is often automatically altered according to the weather. While this is applicable to all anticoagulant therapy, it obtains especially in the above group of post-

partum cases, where the therapeutic problem is to aim at adequate prophylaxis that must of necessity be maintained for a few days, after which the patient will be discharged. In a "hot spell" the initial dosage of these patients might well be 21 mg. of Marcumar, as opposed to the 24 mg. mentioned above. This procedure offers some protection against the hyperreaction we have seen so often in such weather.

Long-Term Marcumar Therapy in Cases of Phlebitis and of Coronary Thrombosis

A spot check was made of the results over a three to four months period in 161 patients under treatment with Marcumar on an outpatient basis. Weekly prothrombin times were determined. Many of these patients had been on Marcumar since 1954. Under such circumstances a greater fluctuation in prothrombin level is to be expected, and we believe it will be found in any careful study of such long-term cases. A definite proportion are classified as "fluctuant," and our criteria for such classification are given below.

Table 6

	10	20	30	40	50	60	70	
E	#######	#######	#######	#####				36 cases
Adeq.	#######	#######	#######	#######	#######	#######	######	69 cases
Fluc.	#######	#######	#######	#######	##			42 cases
R	######							9 cases
S	#####							5 cases
								161 Total

E—Excellent. Above 20 seconds prothrombin time constantly except for one dip to 19 seconds every four months.

Adeq.—Adequate levels. Found to fluctuate only once every two months, that is, to dip into upper teens (18 or 19 sec.). However, 10 cases dipped into the teens once each month. We nevertheless feel that such cases can fall into the adequate group.

Fluc.—Fluctuant. Half-time in teens, but no lower than 18 or 19 seconds. The rest of the time the levels stayed in the 20's.

R—Resistant. Under 19 seconds consistently. Very often, such patients do not respond to increased dosage except that their levels become quite high rather suddenly.

S—Sensitive. Above 35 seconds on one occasion, otherwise adequate. These levels were 54, 42, 37, 45 and 40 seconds.

The initial or loading dosage with out-patients with a normal initial prothrombin time is 18 mg. Marcumar. The patient is brought back at the peak of this action on the third day and twice weekly for two weeks. The usual maintenance dosage is 3 mg. or one tablet daily. This, however, varies from patient to patient, and this dosage may well vary from one tablet every other day to two tablets daily.

In the above series there was one episode of bleeding in an out-patient

who developed bilateral renal pain and associated hematuria. It is interesting that his prothrombin time was never higher than 30 seconds. He made an uneventful recovery on K_1 therapy, and anticoagulants are being continued. From our study of this group we feel that, despite the breakdown showing certain levels of fluctuation, a goodly percentage is adequately protected.

Comparison of Drugs in Out-Patient Therapy

Prothrombin levels were studied using three long-acting coumarins. This series of 288 long-term cases of coronary disease represents the complete record of curves ranging from one to 10 years on anticoagulant therapy.

Although no cases are listed under the heading of sensitivity, this does not mean that in such long-term therapy an occasional high level will not be seen, no matter what drug is used. A numerical listing of patients showing such sensitivity with levels above 35 seconds would be misleading.

The graph on Dicumarol patients in a way shows them in a false light. In our experience, patients showing an initial essential sensitivity seem to do rather well on comparatively small doses of Dicumarol. But it is likewise our experience that patients begun initially on Dicumarol but who demonstrate resistance or fluctuating levels are especially difficult to maintain on this drug. We found that with patients having prothrombin times in the

Table 7

Dicumarol

	10	20	30	40	50	60	70	80	90	100	
E	#####	#									11 (10.5%)
Adeq.	#####	#####	#####	####							39 (37.1%)
Fluc.	#####	#####	#####	#####	#						42 (40.0%)
R	#####	##									13 (12.4%)
S											
											105 Total

Table 8

Cumopyran

	10	20	30	40	50	60	70	80	90	100	
E	##										4 (3.6%)
Adeq.	#####	####									17 (15.3%)
Fluc.	#####	#####	#####	#####	#####	#####	#####	####			76 (68.5%)
R	#####	###									14 (12.6%)
S											
											111 Total

TABLE 9

Marcumar

	10	20	30	40	50	60	70	80	90	100	
E	#####	###									18 (25.0%)
Adeq.	#####	#####	#####	###							34 (47.2%)
Fluc.	#####	####									18 (25.0%)
R	#										2 (2.8%)
S											
											72 Total

KEY—same as preceding out-patient chart.

teens, increased dosage aimed at therapeutic levels would often produce rises to the 30's or higher without ever stopping in the 20's. Transferring such patients to Marcumar therapy almost consistently gave more stable levels. Several years ago those not responding to Dicumarol were placed on Cumopyran. Considering that they were difficult cases, the curves were better. However, as seen in the graph, the percentage of fluctuancy in the curve was quite high. The patients under Marcumar show greater percentages listed as excellent and adequate, and fewer are fluctuant and resistant. We believe, then, that Marcumar is the drug of choice for long-term therapy.

THE USE OF K_1 ORALLY AND INTRAVENOUSLY

The advent of K_1 was a boon to anticoagulant therapy. The quickness and dependability of its action in comparison to that of the older vitamin K compounds are presumably due to an attached phytyl group. Preparations used in our clinic were as follows: oral dosage was in the form of 5 mg. tablets of vitamin K_1; * intravenous K_1 was used as Emulsion of Mephyton.* An ampule of 1 c.c. containing 50 mg. is diluted in 7 c.c. sterile saline and is given at the rate of 1 c.c. per minute.

In anticoagulant therapy the extent and duration of prothrombin depression requiring intervention with K_1 call for experience and judgment.

SUMMARY AND CONCLUSIONS

The effects of the new anticoagulant drug Marcumar have been studied over a period of two years. The records of 1,729 patients treated with Marcumar since June, 1955, are recorded. In our study of the records of hospital patients, they have been classified under coronary disease, phlebitis, postoperative and post partum. We have found that each type of case presents its own difficulties and therapeutic problems. Accordingly, we

* Supplied through the courtesy of Merck and Co.

have cited the actual dosage schedules used by us as a guide in each type of case.

A comparison of Marcumar with Dicumarol and Cumopyran in 288 long-term out-patient cases of coronary disease demonstrated the superiority of Marcumar, even when given to the most difficult cases in the series. An additional spot check of 161 out-patients with phlebitis and coronary disease verified the satisfactory levels obtained with Marcumar. It is our belief, then, that the latter drug is superior to the other long-acting anticoagulants.

As to the so-called short-acting anticoagulants, it is our experience that Hedulin, while obtaining a quick therapeutic blood level, nevertheless presents difficulty after the loading dose and thus tends to give a "peak-and-valley" type of curve. To a less but definite degree Dipaxin presented the same problem.

Marcumar by its prolonged duration of action gives a more stable and satisfactory type of curve. Its advantages far overshadow its initial delayed action. In this respect we stress that any case requiring urgent anticoagulation requires heparin rather than short-acting anticoagulants.

The use of K_1 therapy in correcting high prothrombin times is well recognized, but we stress the practical value of minimal oral doses, even as low as 1.25 mg.: to correct threatening rises over the therapeutic level, yet without causing over-correction.

In this entire series there was no death due to hemorrhage. There was no incidence of bleeding in the 1,080 coronary, phlebitis and postpartum cases. There were three cases of minimal hemorrhage in 400 routine post-operative cases. In 91 postoperative bowel, stomach and gall-bladder cases, despite their known liability to anticoagulant hemorrhage, Marcumar was given, but with extreme caution. One case of moderate gastrointestinal hemorrhage responded to blood transfusion and vitamin K_1 intravenously. Anticoagulants were then stopped in this patient. Ten days after discontinuance the patient died and autopsy revealed massive pulmonary embolism.

It is noteworthy, then, that even in postoperative prophylaxis in bowel, stomach and gall-bladder cases there was no instance of thrombo-embolism while the patient was under therapy.

The goal in anticoagulant therapy is not only adequate depression of blood prothrombin but also and of equal importance the constant maintenance of a stable level. As far as possible there should be no variations into threatened hemorrhage or a veering off into therapeutic inadequacy. In our experience this goal is more closely approached by Marcumar than by other anticoagulants used by us.

ACKNOWLEDGMENTS

Acknowledgment is made to Dr. Leo Pirk, of Hoffman-LaRoche, Inc., Nutley, New Jersey, for the generous supplies of Marcumar.

We are grateful to Merck & Co., Inc., Rahway, New Jersey, for supplies of vitamin K_1.

We are grateful to Mrs. Mary Scott and Miss Arden Kesmodel for technical assistance.

Summario in Interlingua

Depost 1943, plus que 25.000 patientes requirente medication anticoagulante esseva tractate in nostre clinica. Le presente reporto discute le experientias colligite in le casos de 1.732 patientes qui esseva tractate depost junio 1955 con le droga phenprocoumon (Marcumar).

Nos ha studiate le action del droga in patientes hospitalisate—i.e. in casos in que le therapia es frequentemente de duration relativemente breve—e nos ha investigate le action comparative de iste anticoagulante in patientes visitante sub conditiones de tractamento prolongate. In le casos del patientes hospitalisate nos ha credite utile distinguer e discuter separatemente casos de (1) *thrombosis coronari*, (2) *phlebitis*, (3) *prophylaxe postoperatori*, *e* (4) *prophylaxe post parto*. Nos ha trovate que iste varie typos de casos presenta lor difficultates e problemas therapeutic individual de maniera que illos merita un discussion differentiate. Ergo nos ha citate le programmas de dosage usate in le practica in le varie typos de casos e ha includite tabulas que monstra le exacte typo de responsa in le curvas del tempore prothrombinic in le varie classes de patientes.

Marcumar es comparate con altere anticoagulantes usate in 288 patientes visitante con morbo coronari. In iste comparation, attention special es prestate al responsas obtenite con Dicumarol, Cumopyran, e Marcumar.

Il es nostre experientia que le si-appellate anticoagulantes a effectivitate ephemere —per exemplo Hedulina e Dipaxina—es capace a effectuar plus rapidemente le desirate nivello therapeutic in le stato del sanguine sed que illos presenta frequentemente le difficultate que post le administration del dose de cargation illos tende a producer un typo de curva prothrombinic con "culmine e valle."

Le plus perdurante action de Marcumar esseva associate con un plus stabile e ergo plus satisfacente responsa in omne classes de patientes. Su avantages contrabalancia amplemente le retardo initial de su action. In iste connexion nos sublinea le facto que in casos requirente anticoagulation urgente il es heparina plus tosto que anticoagulantes a efficacitate rapide que debe esser administrate. In le caso de Marcumar, le risco del augmento periculose del tempore prothrombinic pote esser obviate per le uso—si necessari—de minimal doses oral de K_1, possibilemente non excedente 1,25 mg. Isto reduce le nivello sed non causa hyper-correction. Assi, le uso supplementari de doses minimal de K_1 resulta, in nostre opinion, in que le action prolongate de Marcumar es de facto un avantage ab le puncto de vista del obtention de un curva stabile.

Le serie integre includeva nulle caso de morte in consequentia de hemorrhagia. Il es a notar que iste constatation vale etiam pro le difficilissime casos del categoria "postoperatori" con chirurgia intestinal, gastric, e de vesica biliari. A causa del cognoscite risco de hemorrhagias associate con le uso de anticoagulantes in tal casos, multe autores include los in le lista del conditiones in que iste drogas es contraindicate. In 91 tal casos, Marcumar esseva administrate con le plus meticulose circumspection. Nulle thrombo-embolismo occurreva durante le curso del therapia. Esseva incontrate un caso de moderate hemorrhagia gastrointestinal, sed isto respondeva a transfusion de sanguine con administration intravenose de vitamina K_1. Inter 400 routinari casos postoperatori, tres habeva un hemorrhagia minimal. Nulle incidentia de sanguination esseva incontrate in 1.080 casos coronari, phlebitic e post parto.

Le objectivo de therapia anticoagulante es non solmente le obtention de un adequate depression del prothrombina del sanguine sed etiam—e isto es non minus importante—le effectuation de un mantenentia constante de un nivello stabile. In tanto que possibile, le prothrombina non debe variar de maniera a producer le risco de hemorrhagia o a descender in inadequatia therapeutic. In nostre experientia iste objectivo es realisabile plus efficacemente per medio de Marcumar que per le altere anticoagulantes que nos ha usate.

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CHANGING CONCEPTS IN THE TREATMENT OF PULMONARY TUBERCULOSIS *

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The therapy of tuberculosis has undergone a remarkable change since the advent of antimicrobials, particularly isoniazid. Cornerstones of past treatment have in many instances been relegated to ancillary rôles. The changing concepts which, in our opinion, have contributed to a decrease in the incidence of therapeutic failures are:

1. "Adequate" combined drug therapy.
2. Determination of the dosage of isoniazid by assay methods to insure adequate levels of the antimicrobially active drug in vivo.
3. Physical activity as a basic principle of treatment.
4. Surgery for the significant residual pulmonary lesion.

"Adequate" Combined Drug Therapy

There is widespread acceptance of the principle of combined antimicrobial therapy, a principle first clinically discussed by Karlson [1] and Dunner,[2] and later broadened by Tempel.[3] The latter found that intermittent streptomycin, combined with daily PAS, was clinically more effective than when either drug was used alone. Likewise, there was a decreased incidence of mutants resistant to either drug.

When isoniazid (INH) was first introduced, coöperative groups began to investigate its therapeutic potentialities both singly and in various regimens of combined therapy. Jimenez [4] feels that isoniazid, at the daily dose of 5 and 10 mg./kg. in previously untreated cases, has a therapeutic effectiveness similar to the combination of isoniazid-streptomycin or isoniazid-PAS. Eighty-three per cent of 34 far advanced, previously untreated cases, after two years of observation, had a reversal of infectiousness, and in 71% all cavities were closed. Tucker [5] also felt that INH alone was comparable with INH-streptomycin (the latter drug twice weekly) and streptomycin-PAS in noncavitary or single cavitary cases.

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Our findings with streptomycin, 1.0 gm. three times weekly, and INH, 8–16 mg./kg./day, are somewhat similar to those of Jimenez and Tucker with INH alone, in that 72% of the patients had negative sputa at the end of four months. Twenty-six per cent remained sputum-positive and excreted INH-resistant organisms, and 2% still were excreting INH-susceptible organisms. Streptomycin-susceptible organisms were excreted in all positive cases for at least four months after the emergence of INH-resistant mutants. If the dosage of one drug in a two-drug program is inadequate, organism resistance to the drug present in adequate concentration develops first. The presence of streptomycin-susceptible organisms in the cases where inadequate streptomycin (2 to 3 gm./wk.) was used suggests that certain antagonistic factors (such as desoxyribonucleic acid) bind the streptomycin before it can exert any antimicrobial action. This prevention of drug action may explain the failure of streptomycin-resistant mutants to develop sooner. The British Medical Research Council [6-8] showed that higher doses of streptomycin resulted in fewer cases excreting INH-resistant organisms on their combined INH-streptomycin regimen. Thus the dosage of streptomycin would have to be increased before adequate combined drug therapy could be achieved. We shall describe here a high dosage INH-streptomycin treatment program: a chemotherapeutic regimen which, when combined with physical activity, gave us good and consistently reproducible results in all patients excreting tubercle bacilli susceptible to both drugs (SM, INH).

Determination of the Dosage of Isoniazid by Assay Methods to Insure Adequate Levels of the Antimicrobially Active Drug in Vivo

Since INH is one antimicrobial agent that is included in almost every therapeutic regimen, it is important that the problem of dosage be reviewed. It has been shown that INH is biochemically altered in vivo, and that patients vary in their capacity to form end products which possess no antimicrobial activity. In spite of these known variations, popular usage has decreed that 300 mg., or 3 to 5 mg./kg./day, of INH is effective therapy. In nearly 50% of the patients studied at National Jewish Hospital by means of a microbiologic assay method, such dosage proved to be inadequate as determined by the types of mutants excreted by chemotherapeutic failures.[9] Retrospective analysis of 56 patients excreting INH-resistant variants has shown that those whose INH-resistant organisms were catalase-positive were the patients who achieved a low concentration of free INH. This substantiates the impression that there is a relationship between the type of mutants, the serum INH level and low dosage.

Various chemical methods have been described for the specific determination of serum INH levels, but these have been inadequate, since they are not sufficiently sensitive to measure the biologically active moiety resulting from conventional loading dosages.[10] Middlebrook [11] and Morse [12] have

devised reproducible microbiologic assay methods which clearly measure the antimicrobially active INH present in the serum at the end of a six-hour tolerance test. The results of this test have served to define the INH dosage necessary to achieve an adequate serum level.

Materials and Methods of the Microbiologic Assay of Middlebrook [11]

For two days prior to the tolerance test the patient receives INH, 8 mg./kg./day. Except for insulin, no medication should be given after 12:00 midnight. At 9:00 a.m., 4 mg. INH/kg. are given. At 3:00 p.m., plus or minus 15 minutes, enough blood is withdrawn aseptically to yield at least 1 ml. of sterile serum. One milliliter of serum is added to 9 ml. of oleic acid-albumin liquid medium (ST–T), containing 10 μg. of para-aminobenzoic acid and 25 μg. of penicillin G per milliliter. From this tube of 1:10 serum dilution, 2.5 ml. aliquots of serum dilutions of 1:10, 1:20 and 1:40 are prepared in duplicate in ST–T medium in screw-capped culture tubes. Each of six tubes for any one determination is then inoculated with 0.1 ml. of a fully grown, dispersed stock culture of an INH-susceptible, streptomycin-resistant strain of tubercle bacilli (H37RvS–RSM) grown in ST–T medium containing 0.05% Tween 80® and 10 μg. streptomycin per milliliter. The inoculated tubes, together with a standard control test of susceptibility of the strain to known concentrations of INH (0.0, 0.02, 0.04 and 0.08 μg. of INH/ml.), in 10% normal serum, are incubated at 36° C. After five days a Ziehl-Neelsen stained smear from each tube is prepared and the tubercle bacilli are examined for loss of acid-fastness. This is a specific test for antimicrobially-active INH, as neither human sera nor any known antimicrobial agent other than INH has this effect on multiplying tubercle bacilli.

Table 1

Microbiologic Assay Serum INH Level Determined by Six Hour Tolerance Test

*Serum Dilution	Acid-Fastness	Biol. Active INH Present	R** INH/d	R** B_6/d
1:40	Lost	1.6 mcg/ml.	4 mg./kg.	25 mg.
1:20	Lost	0.8 mcg/ml.	8 mg./kg.	50 mg.
1:10	Lost	0.4 mcg/ml.	16 mg./kg.	100 mg.
1:10	Not lost	<0.4 mcg/ml.	16 mg./kg. +10 gm. PAS or PABA	100 mg.

* Determined with 4 mg. INH/kg. loading dose.
** Recommended daily dosage of INH and pyridoxine (B_6) for each INH level.

Interpretation (table 1): Loss of acid-fastness at 1:40 dilution (1.6 μg./ml. biologically active INH is present at the end of the six-hour period): In these patients, a more-than-effective INH level can be maintained with

4 mg./kg./day. Loss of acid-fastness at 1:20 dilution (0.8 μg./ml. biologically active INH present): Therapeutic level of INH can easily be maintained with INH, 8 mg./kg./day. Loss of acid-fastness at 1:10 dilution (0.4 μg./ml. biologically active INH present): Therapeutic level can be maintained with 16 mg. INH/kg./day. No loss of acid-fastness at 1:10 dilution (less than 0.4 μg./ml. biologically active INH present): This is an inadequate level, but on the addition of 10 gm. of para-aminosalicylic acid or para-aminobenzoic acid [13] per day in divided doses, an adequate level of biologically active INH can be achieved with 16 mg. INH/kg./day. Probably para-aminosalicylic acid or para-aminobenzoic acid elevates the INH level by competing with INH for the acetylating mechanism. All rapid inactivators of INH should have a repeat tolerance study done with an 8 mg./kg. loading dose of INH. If the serum level is still unsatisfactory, in addition to the 8 mg./kg. loading dose of INH, 2.5 gm. of para-aminosalicylic acid or para-aminobenzoic acid should be given at 9:00 a.m. and at 12:00 noon. In many instances the therapeutic superiority of INH plus PAS over INH alone may be attributable not only to the antimicrobial activity of PAS itself

TABLE 2

Microbiologic Assay Distribution of INH Tolerance Levels in 494 Patients*

Biologically Active INH Present	Number	Per Cent
≥1.6 mcg/ml. Slow inactivators	160	32
0.8 mcg/ml.	99	20
0.4 mcg/ml.	57	12
<0.4 mcg/ml. Rapid inactivators	178	36
Total	494	100

* INH loading dose was 4 mg./kg.

but also to its aid in delivering a higher concentration of biologically active INH to the multiplying organisms.

Pyridoxine, in various dosages, is included to lessen the incidence of significant isoniazid neuropathy. Fifty milligrams of pyridoxine a day are given to patients who receive 8 mg./kg./day of INH, and 100 mg. of pyridoxine is the recommended initial dosage when 16 mg./kg./day of INH are given. Dosage of pyridoxine should be increased if toxic symptoms referable to INH are observed. Pyridoxine, except in massive dosage, does not interfere with the chemotherapeutic activity of INH in experimental animals, nor does its administration have a detectable effect on INH serum levels determined by microbiologic assay.[14, 15]

All patients presently admitted to the National Jewish Hospital have a microbiologic assay before starting INH therapy. In 494 cases, the following distribution was observed (table 2): ≥ 1.6 μg./ml. biologically active INH, *the slow inactivator,* 32%; 0.8 μg./ml., 20%; 0.4 μg./ml., 12%; < 0.4 μg./ml., *the rapid inactivator,* 36%. These studies would suggest that only those cases achieving ≥ 0.4 μg./ml. of biologically active INH, or 64% of

the total, would have had effective INH therapy on the standard dosage of 300 mg./day. Because the ability to metabolize INH does not vary significantly during treatment, the microbiologic assay is performed only twice in those individuals initially showing an effective serum level.

If assay for free INH is not available, then the highest INH dosage compatible with a minimum of toxic side effects should be used. Between 8 and 16 mg./kg./day of INH, plus 10 gm. of para-aminosalicylic acid or para-aminobenzoic acid, provide adequate INH therapy for over 95% of white Americans.

Physical Activity as a Basic Principle of Treatment

Prior to the antimicrobial drugs, the goal of effective treatment in tuberculosis was to force the organism into a metabolically dormant state. This uneasy truce between host and parasite was often achieved by strict bed-rest plus artificial intrapleural pneumothorax, pneumoperitoneum, paralysis of the diaphragm, extrapleural pneumothorax with or without plombage material, or a classic thoracoplasty. For the last four years at our hospital there has been an intentional emphasis on physical activity as an important part of treatment. As previously described,[16] this has been effected in the treatment of nearly all hospitalized patients at the National Jewish Hospital who were ill with tuberculosis and who were receiving INH alone, or the combination of INH-streptomycin and/or PAS. Usually, ambulation has been started as soon as clinical signs of toxicity have subsided.

The rationale for physical activity during chemotherapy of tuberculous patients, regardless of anatomic extent of disease or bacteriologic status, stems from the following findings: In vitro studies have clearly shown that streptomycin [17, 18] and INH [19, 20] are effective as bactericidal agents only against multiplying populations of tubercle bacilli. Since tubercle bacilli are strict aerobes, requiring oxygen for multiplication, physical activity insures this increased oxygen uptake both by means of increased movement of the lungs and by improved cavity drainage. As a result, the metabolically active, drug-susceptible state of the tubercle bacilli is maintained because the increased molecular oxygen keeps the organisms in a proliferating phase.

Until agents are available which have a direct sterilizing activity against metabolically dormant tubercle bacilli, rest treatment for patients excreting drug-susceptible organisms is, in our view, probably contraindicated. The goal of chemotherapy should be to avoid the resting phase and to maintain the tubercle bacilli in the state of greatest physiologic drug-susceptibility.[21]

In 1926, even before the antimicrobial era, Stocks and Karn [22] challenged the concept of bed-rest in pulmonary tuberculosis as a form of treatment. They observed 2,794 consecutive cases for six years and concluded that the out-patients were more likely to maintain their clinical improvement than were the sanatorium-treated cases. Although cavities closed at an accelerated pace while the patient was on bed-rest, the relapse rate was higher fol-

lowing his return to activity. It is known that the material inspissated in closed cavities contains dormant parasites, many of which possess the latent ability to return to the metabolically active state. Increased physical activity, we have long believed, promotes cavity drainage and tends to prevent the inspissation of the cavity content.

Tyrell [23] observed no differences in the erythrocyte sedimentation rate, sputum conversion and over-all radiographic improvement at six months between 45 hospitalized patients treated with strict bed-rest plus chemotherapy, and 46 out-patients treated with chemotherapy alone. It seems most significant that cavity closure, probably secondary to blockade of the bronchocavitary junction, was more common in the patients on strict bed-rest than it was in the ambulant out-patients. Controlled studies by Wier [24] and Hirsch [25] have confirmed our impression [16] that the ambulatory patient with chemotherapy coverage showed the same early clinical course as the bed-rest patient.

The ultimate value of the early ambulation program will need to be correlated with the relapse rate that may occur within three to five years after antimicrobial chemotherapy has been stopped. If, as we believe, early ambulation assists in decreasing bacterial population by promoting drainage and elimination of the organisms and cavity content, the relapse rate should be less in this group. Finally, physical activity obviates the depressing psychologic effects of a long period of enforced idleness in the company of patients similarly afflicted. This promotes rehabilitation—by fostering positive attitudes which enable the patient to consider his disease not a disabling one, but rather one over which he can develop a sense of mastery.

The patient with extensive disease, excreting drug-resistant organisms and considered to be a chemotherapeutic failure, presents a different problem. Here, bed-rest, with or without collapse procedures or thoracic surgery, and with INH therapy in particular, are appropriate. If isoniazid does nothing else, it protects against the potential reactivation caused by susceptible organisms coming from previously closed lesions. Collapse therapy, on the other hand, promotes the metabolically dormant state of such resistant organisms by mechanically reducing the access of molecular oxygen to the infected area.

Case Reports

Case 1. This patient was admitted to National Jewish Hospital in June, 1955, with extensive bilateral disease. His sputum on admission contained organisms resistant to INH but susceptible to streptomycin. After seven months of combined streptomycin, PAS and INH therapy his organisms manifested a high degree of resistance to all three drugs. In January, 1956, while on 8 mg./kg./day of INH and 100 mg. of pyridoxine daily, a left artificial pneumothorax was initiated in an effort to close a cavity in the left lower lobe so that surgery could be performed on the right (figure 1). Within three months the cavity closed by inspissation, and the right upper lobe was successfully resected (figure 2). At this time the sputum converted to negative. The inspissated left lower lobe cavity-bearing area was removed in August,

1956. Two months later the patient was discharged from the hospital still sputum-negative for acid-fast bacilli (figure 3). Of additional interest was the observation that the grumous material in the inspissated cavity in the left lower lobe had the same level of microbiologically active INH as did the serum.

Although physical activity has become an integral part of our treatment program, the need for hospitalization and careful observation during the ini-

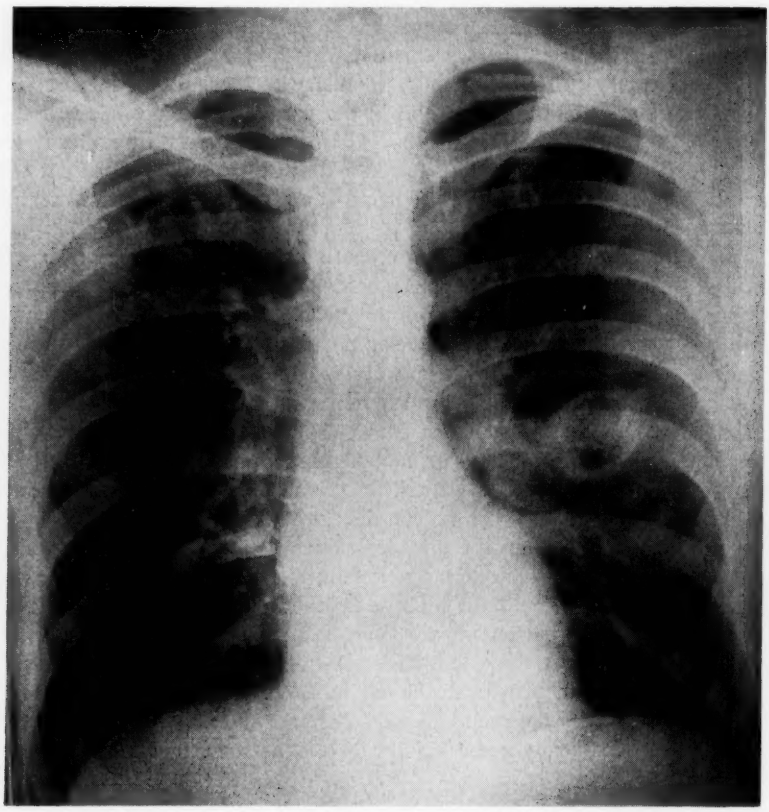

FIG. 1. Cavity-bearing areas are observed in both the right upper lobe and the upper portion of the lower lobe on the left. Note the beginning pneumothorax on the left side.

tial phases of therapy should not be underestimated. Aside from the obvious advantage of isolating the infectious case, there are many advantages secondary to initiating and controlling treatment in a hospital milieu. Adequate dosage of INH, under ideal circumstances, requires that assay studies be done on the serum of all patients. Failure to achieve an effective drug level can result either in no antibacterial effect at all, or in the emergence of the more undesirable type of INH-resistant, catalase-positive mutants.[9] If com-

bined drug therapy is to be adequate, the drug susceptibilities of the organism must be known prior to the initiation of therapy. Resistance appears to be an all-or-none phenomenon. Once drug resistance has been established, an increase in the amount of the therapeutic agent to which there is resistance is rarely effective. Since there is a close relationship between the antimicrobial therapeutic dose and the toxic dose, frequent observation is neces-

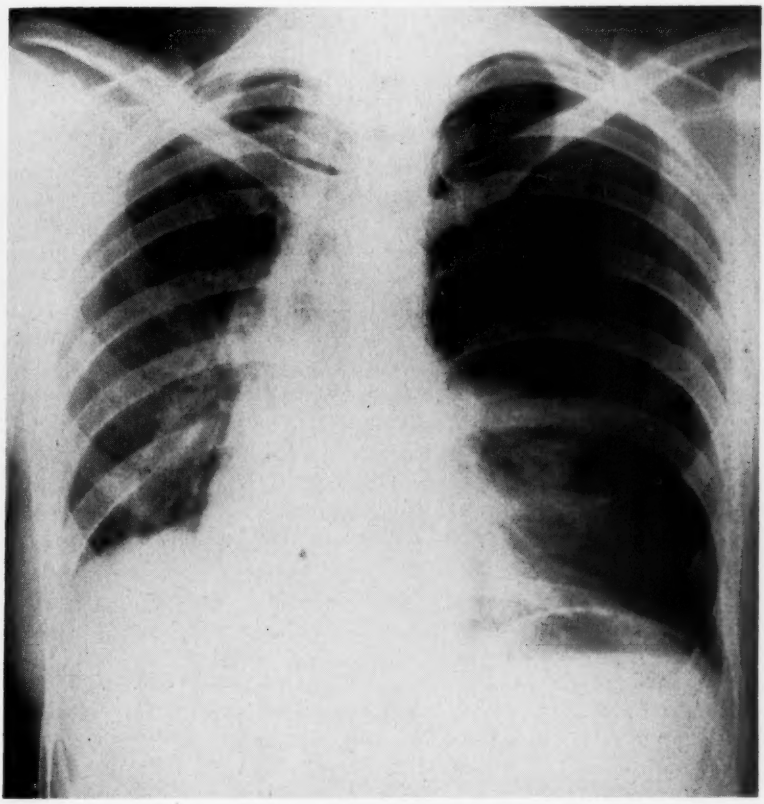

FIG. 2. The cavity-bearing area in the right upper lobe has been resected. There has been an inspissation of the cavity content on the left as a result of the pneumothorax.

sary to detect incipient toxic drug reactions. Finally, repeated sputum and x-ray studies serve as a guide to proper antimicrobial management. One may assume that the therapy is effective when the sputum smears and cultures show a gradual decline in the bacterial population prior to becoming negative. On the other hand, a precipitous conversion to negativity suggests a bronchocavitary block, implying that chemotherapy has not had sufficient opportunity to have its maximal effect.

Practical Clinical Results of Application of These Observations

As a result of the above studies the following program of therapy was formulated as a pilot study at the National Jewish Hospital: All patients excreting acid-fast bacilli in their sputum which were susceptible to INH and streptomycin were treated with streptomycin, 15 to 30 mg./kg./day, for 90 days or more if their sputum had not become negative on culture.

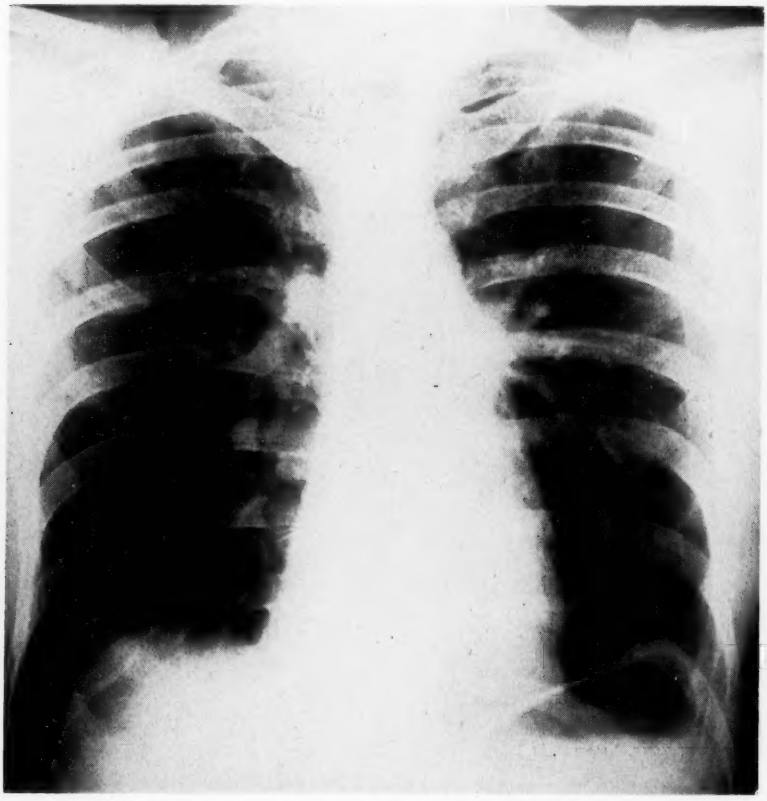

Fig. 3. This is approximately six months after the cavity-bearing area on the left was resected and the lung permitted to reëxpand. No disease-bearing areas are noted.

Daily INH, in a dosage determined by the microbiologic assay method, was given for 18 months. Pyridoxine, 50 to 100 mg. daily, was given for the same period as the INH. PAS, or PABA, 10 gm. per day, in divided doses, was added to this program when the patient proved to be a rapid INH inactivator.

From October 1, 1954, until June 5, 1956, 369 adult patients with pulmonary tuberculosis were consecutively admitted to the National Jewish

Hospital. Of this number, 124 were excreting organisms resistant to one or both drugs (SM, INH). The sputa from 116 were never positive on smear or culture at any time, or they yielded a growth insufficient for reliable drug-susceptibility evaluation. There were eight patients who were excreting "atypical" tubercle bacilli. The remaining 121 patients were shown to be excreting tubercle bacilli which were susceptible to 2.0 μg. of streptomycin per milliliter and to 0.2 μg. of isoniazid per milliliter.* Eight of these 121 cases were lost from the study before completing six months of treatment. Two died of nontuberculous causes.

The first 46 cases (table 3) had bilateral moderate to far advanced pulmonary tuberculosis—at least one cavity not less than 1 cm. in greatest diameter, and sputum-positive on smear (at least 1 AFB per oil immersion field). Typical tubercle bacilli were recovered on culture, and the organisms were susceptible to streptomycin, 2.0 μg./ml., and INH, 0.2 μg./ml. Daily streptomycin was given for 90 days or more, as has been described, and regardless of the microbiologic assay results, INH, 16 mg./kg./day, was used. All patients except those with severely restricted cardiopulmonary function were up and about, physically out of bed for 10 to 12 hours daily.

Prior to initiation of combined streptomycin-INH therapy, cases 1 through 31 were primed with 21 days' PZA, 2.5 gm. per day, and cortisone, 100 mg. per day. This "preparation" was based on the concept that reduction in the number of tubercle bacilli, combined with the steroid effect of reducing the inflammatory reaction, particularly at the bronchocavitary junction, might augment the initial impact of the subsequent high dosage therapy. Because this method of "preparation" was under investigation, cases 32 to 46, although comparable in severity with the abovementioned cases, did not receive the PZA and steroid compounds. They did, however, receive INH, 16 mg./kg./day and streptomycin daily. In a separate paper an evaluation of the usefulness of the PZA and steroid therapy will be reported.

Cases 47 to 121 (table 3) were not so extensively involved as the preceding cases. Cavities were not so large, and the sputum, although not always positive on concentrated smear, was positive initially on culture. The organisms were typical tubercle bacilli on culture, and they were susceptible to streptomycin, 2.0 μg./ml. and to INH, 0.2 μg./ml. These cases were treated with daily INH, dosage determined by the microbiologic assay, and with streptomycin for at least 90 days. Within six months of the start of treatment with drug therapy only, all of the 113 cases studied had become sputum-negative. All cases became negative before any emergence of resistance was noted. Since this was not a controlled study, we compared our

* At the National Jewish Hospital, populations of tubercle bacilli are considered to be susceptible to streptomycin and isoniazid if, on direct testing on 7H-10 solid medium, less than 1% of the numbers of organisms yielding colonies on the control can grow on the same culture medium containing either 0.2 μg. of isoniazid per milliliter or 2.0 μg. of streptomycin per milliliter.

TABLE 3

Result of High INH-High SM Treatment in 121 Selected Cases (1, 2, 3)

Case Number	Extent of Disease on Admission (X-ray)	Cavity	Cavity Size, Longest Dimension in Cm.	Age in Years	Sex	Race	Bacteriology Before Treatment		Bacteriologic Status After Treatment Started					
									1–4 Months		5–8 Months		9–12 Months	
							S	C	S	C	S	C	S	C
1.	MA,	Bil,	Single	1–2	19	M	W	+	+	0	0	0	0	0	0
2.	FA,	Bil,	Single	4.0–7.5	31	M	W	+	+	0	0	0	0	0	0
3.	MA,	Bil,	Mult.	1–2	22	M	W	+	+	0	0	0	0	—	—
4.	MA,	Bil,	Mult.	2.5–3.5	45	F	W	+	+	0	0	0	0	—	—
5.	MA,	Bil,	Mult.	2.5–3.5	28	M	W	+	+	0	0	0	0	—	—
6.	MA,	Bil,	Mult.	2.5–3.5	45	M	W	+	+	0	0	0	0	0	0
7.	MA,	Bil,	Mult.	2.5–3.5	33	F	W	+	+	0	0	0	0	0	0
8.	MA,	Bil,	Mult.	2.5–3.5	60	F	W	+	+	0	+	0	0	0	0
9.	MA,	Bil,	Mult.	4.0–7.5	21	F	W	+	+	0	0	0	0	0	0
10.	MA,	Bil,	Mult.	4.0–7.5	32	F	W	+	+	+	0	0	0	0	0
11.	FA,	Bil,	Mult.	2.5–3.5	29	F	W	+	+	0	0	0	0	0	0
12.	FA,	Bil,	Mult.	2.5–3.5	34	M	W	+	+	+	+	0	0	0	0
13.	FA,	Bil,	Mult.	2.5–3.5	25	M	W	+	+	+	+	0	0	0	0
14.	FA,	Bil,	Mult.	2.5–3.5	38	M	W	+	+	+	0	0	0	0	0
15.	FA,	Bil,	Mult.	2.5–3.5	40	M	W	+	+	+	+	0	0	0	0
16.	FA,	Bil,	Mult.	4.0–7.5	27	M	W	+	+	0	0	0	0	0	0
17.	FA,	Bil,	Mult.	4.0–7.5	42	M	W	+	+	0	+	0	0	0	0
18.	FA,	Bil,	Mult.	4.0–7.5	41	F	W	+	+	+	0	0	0	0	0
19.	FA,	Bil,	Mult.	4.0–7.5	56	M	W	+	+	+	+	0	0	—	—
20.	FA,	Bil,	Mult.	8.0+	49	M	N	+	+	0	0	0	0	0	0
21.	FA,	Bil,	Mult.	8.0+	32	M	N	+	+	+	+	0	0	0	0
22.	FA,	Bil,	Mult.	8.0+	45	M	W	+	+	+	+	0	0	0	0
23.	FA,	Bil,	Mult.	8.0+	40	M	W	+	+	+	+	0	0	0	0
24.	FA,	Bil,	Mult.	8.0+	45	F	W	+	+	+	+	0	0	0	0
25.	MA,	Bil,	Mult.	2.5–3.5	31	F	W	+	+	+	+	0	0	0	0
26.	FA,	Bil,	Mult.	2.5–3.5	66	M	W	+	+	+	+	0	0	0	0
27.	FA,	Bil,	Mult.	4.0–7.5	23	F	Ind.	+	+	+	0	0	0	0	0
28.	FA,	Bil,	Mult.	4.0–7.5	68	M	W	+	+	0	+	0	0	—	—
29.	FA,	Bil,	Mult.	4.0–7.5	41	M	W	+	+	+	+	0	0	0	0
30.	FA,	Bil,	Mult.	4.0–7.5	35	M	W	+	+	+	0	0	0	0	0
31.	FA,	Bil,	Mult.	8.0+	44	F	N	+	+	+	+	0	0	0	0
32.	MA,	Bil,	Single	1–2	28	M	W	+	+	0	0	0	0	0	0
33.	FA,	Bil,	Single	4.0–7.5	57	F	W	+	+	+	+	0	0	—	—
34.	MA,	Bil,	Mult.	1–2	80	F	W	+	+	0	0	0	0	—	—
35.	MA,	Bil,	Mult.	4.0–7.5	51	M	W	+	+	+	0	0	0	0	0
36.	FA,	Bil,	Mult.	2.5–3.5	32	M	N	+	+	0	+	0	0	—	—
37.	FA,	Bil,	Mult.	2.5–3.5	56	M	W	+	+	+	+	0	0	0	0
38.	FA,	Bil,	Mult.	4.0–7.5	56	M	W	+	+	0	0	0	0	—	—
39.	FA,	Bil,	Mult.	4.0–7.5	40	M	W	+	+	0	+	0	0	0	0
40.	FA,	Bil,	Mult.	4.0–7.5	45	M	W	+	+	+	+	0	0	+	0
41.	MA,	Bil,	Single	2.5–3.5	45	M	W	+	+	0	0	0	0	—	—
42.	MA,	Bil,	Mult.	1–2	66	M	W	+	+	0	0	0	0	—	—
43.	MA,	Bil,	Mult.	1–2	28	M	Ch.	+	+	+	+	0	0	0	0
44.	MA,	Bil,	Mult.	2.5–3.5	63	F	W	+	+	+	+	0	0	—	—
45.	MA,	Bil,	Mult.	2.5–3.5	27	F	W	+	+	+	+	0	0	—	—
46.	FA,	Bil,	Mult.	4.0–7.5	22	M	N	+	+	0	0	0	0	—	—
47.	MI,	Uni,	—	—	25	F	W	+	+	+	+	—	—	—	—
48.	MI,	Uni,	Single	1–2	27	M	W	+	+	0	0	—	—	—	—
49.	MI,	Bil,	—	—	30	M	Or.	0	+	0	0	—	—	—	—
50.	MI,		Single	1–2	57	M	N	0	+	0	+	—	—	—	—

TABLE 3 (*Continued*)

Case Number	Extent of Disease on Admission (X-ray) Cavity	Cavity Size, Longest Dimension in Cm.	Age in Years	Sex	Race	Bacteriology Before Treatment		Bacteriologic Status After Treatment Started					
								1–4 Months		5–8 Months		9–12 Months	
						S	C	S	C	S	C	S	C
51.	MA, Bil, —	—	34	F	W	+	+	0	0	—	—	—	—
52.	FA, Bil, Mult.	2.5–3.5	41	M	W	+	+	—	—	—	—	—	—
53.	FA, Bil, Mult.	8.0+	28	F	W	+	+	+	+	—	—	—	—
54.	FA, Bil, Mult.	—	75	M	W	+	+	—	—	—	—	—	—
55.	MI, Uni, Single	1–2	40	F	W	0	+	0	+	0	0	—	—
56.	MI, Uni, Single	4.7–7.5	23	F	N	0	+	0	+	0	0	0	0
57.	MI, Uni, —	—	46	F	W	0	+	+	0	0	0	0	0
58.	MI, Uni, —	—	20	F	W	+	+	+	0	0	0	—	—
59.	MI, Uni, —	—	36	M	W	+	+	0	0	0	0	—	—
60.	MI, Uni, —	—	23	F	W	+	+	0	0	0	0	—	—
61.	MI, Uni, —	—	35	F	W	0	+	+	+	0	0	—	—
62.	MI, Uni, —	—	24	F	W	+	+	+	+	0	0	0	0
63.	MI, Bil, —	—	24	M	Or.	+	+	0	0	0	0	—	—
64.	MI, Bil, —	—	32	F	W	+	+	0	0	0	0	0	0
65.	MA, Uni, Single	0.5	26	M	W	0	+	0	0	0	0	—	—
66.	MA, Uni, Single	1–2	48	M	W	0	+	0	+	0	0	0	0
67.	MA, Uni, Single	1–2	24	F	W	0	+	0	+	0	0	0	0
68.	MA, Uni, Single	1–2	34	M	W	+	+	+	+	0	0	0	0
69.	MA, Uni, Single	1–2	44	F	W	+	+	+	+	0	0	—	—
70.	MA, Uni, Single	2.5–3.5	22	M	Or.	+	+	0	0	0	0	0	0
71.	MA, Uni, Single	2.5–3.5	19	F	W	+	+	0	0	0	0	0	0
72.	MA, Uni, Single	2.5–3.5	36	M	W	+	+	+	+	0	0	—	—
73.	MA, Uni, Single	2.5–3.5	32	F	W	+	+	+	+	0	0	—	—
74.	MA, Uni, Single	2.5–3.5	19	M	W	+	+	+	+	0	0	0	0
75.	MA, Uni, Single	2.5–3.5	30	M	W	+	+	+	+	0	0	0	0
76.	MA, Uni, Single	4.0–7.5	47	M	W	+	+	0	0	0	0	0	0
77.	MA, Uni, Single	4.0–7.5	30	F	W	+	+	0	0	0	0	0	0
78.	MA, Uni, Single	4.0–7.5	23	M	W	+	+	+	+	0	0	0	0
79.	MA, Uni, Single	—	49	M	W	+	+	0	0	0	0	—	—
80.	MA, Uni, Mult.	1–2	17	F	W	+	+	+	+	0	0	0	0
81.	MA, Uni, Mult.	2.5–3.5	42	M	W	+	+	+	+	0	0	—	—
82.	MA, Uni, Mult.	—	40	F	N	+	+	0	+	0	0	—	—
83.	MA, Uni, —	—	56	M	W	0	+	0	0	0	0	—	—
84.	MA, Uni, —	—	64	M	W	+	+	0	0	0	0	—	—
85.	MA, Uni, —	—	38	M	W	+	+	0	0	0	0	—	—
86.	MA, Uni, —	—	39	M	W	+	+	0	+	0	0	—	—
87.	MA, Uni, —	—	40	F	W	+	+	+	+	0	0	—	—
88.	MA, Bil, Single	1–2	50	F	N	0	+	0	0	0	0	—	—
89.	MA, Bil, Single	1–2	45	M	W	0	+	+	0	0	0	—	—
90.	MA, Bil, Single	1–2	49	M	N	+	+	+	+	0	0	—	—
91.	MA, Bil, Single	1–2	36	F	W	+	+	+	+	0	0	—	—
92.	MA, Bil, Single	2.5–3.5	29	M	Or.	0	+	0	+	0	0	—	—
93.	MA, Bil, Single	—	38	F	W	+	+	+	+	0	0	—	—
94.	MA, Bil, Single	—	27	M	W	+	+	+	+	0	0	—	—
95.	MA, Bil, Mult.	4.0–7.5	47	F	W	+	+	+	+	+	0	—	—
96.	MA, Bil, Mult.	—	43	M	W	+	+	+	+	0	0	—	—
97.	MA, Bil, Mult.	—	56	F	W	+	+	+	+	0	0	—	—
98.	MA, Bil, —	—	24	F	Or.	0	+	0	0	0	0	—	—
99.	MA, Bil, —	—	59	M	W	+	+	0	0	0	0	—	—
100.	MA, Bil, —	—	61	M	W	+	+	0	0	0	0	—	—
101.	MA, Bil, —	—	43	M	N	+	+	0	+	0	0	0	0
102.	MA, Bil, —	—	36	F	W	+	+	+	+	0	0	0	0

TABLE 3 (*Continued*)

Case Number	Extent of Disease on Admission (X-ray) Cavity	Cavity Size, Longest Dimension in Cm.	Age in Years	Sex	Race	Bacteriology Before Treatment		Bacteriologic Status After Treatment Started					
								1–4 Months		5–8 Months		9–12 Months	
						S	C	S	C	S	C	S	C
103.	MA, Bil, —	—	63	F	W	+	+	+	+	0	0	0	0
104.	MA, Bil, —	—	25	F	W	+	+	+	+	0	0	0	0
105.	FA, Uni, Single	1–2	44	M	W	0	+	0	+	0	0	0	0
106.	FA, Uni, Single	2.5–3.5	28	M	W	+	+	0	+	0	0	—	—
107.	FA, Uni, Single	2.5–3.5	26	M	W	+	+	+	+	0	0	—	—
108.	FA, Uni, Single	—	46	M	W	+	+	+	+	0	0	0	0
109.	FA, Uni, Mult.	1–2	48	M	W	0	+	0	+	0	0	0	0
110.	FA, Uni, Mult.	1–2	44	M	W	+	+	+	+	0	0	0	0
111.	FA, Uni, Mult.	2.5–3.5	29	M	N	+	+	0	0	0	0	—	—
112.	FA, Uni, Mult.	2.5–3.5	35	M	W	+	+	0	+	0	0	—	—
113.	FA, Bil, Single	1–2	58	M	N	+	+	+	+	0	0	—	—
114.	FA, Bil, Single	2.5–3.5	18	F	W	+	+	+	+	0	0	—	—
115.	FA, Bil, Single	—	52	M	W	+	+	0	+	0	0	—	—
116.	FA, Bil, Single	—	30	F	W	+	+	+	+	0	0	0	0
117.	FA, Bil, —	—	15	F	N	0	+	0	0	0	0	0	0
118.	FA, Bil, —	—	48	M	W	+	+	+	+	0	0	0	0
119.	FA, Bil, —	—	36	M	W	+	+	+	+	0	0	0	0
120.	FA, Bil, Mult.	4.0–7.5	22	F	N	+	+	+	+	0	0	—	—
121.	FA, Bil, Mult.	—	46	M	W	+	+	+	+	0	0	0	0

S = smear; C = culture; + = positive; 0 = negative.

(1) Every adult patient admitted between 10-1-54 and 6-5-56 with bilateral, moderate to far advanced pulmonary tuberculosis, with at least one cavity not less than 1.0 cm. in greatest diameter, with sputum positive on concentrated smear (at least one AFB per oil immersion field) and on culture, with typical tubercle bacilli susceptible to SM 2.0 mcg/ml. and to INH 0.2 mcg/ml., with no collapse or surgery until the sputum had been negative for at least four months, and who were treated for six months or longer.

(2) Cases 47–121 were not as extensively involved as the preceding cases. The cavities were not as large and the sputa, although not always positive on smear, were positive initially on culture. The organisms were typical and sensitive to streptomycin and INH.

(3) Cases 47 and 54 died nontuberculous. Cases 48 to 53 inclusive were discharged against medical advice.

first 46 cases with a similar group of extensively involved cases from the basic regimens of the Veterans Administration coöperative study.[26] It was noted that only 85% sputum conversion on culture was achieved with the best Veterans Administration program (PAS-INH) of chemotherapy by the five-to-eight-month report period (table 4). To our knowledge, there has been only one bacteriologic relapse in our series of 113 (case 77). After seven months of treatment he was discharged from the hospital with a cavity-bearing area in the right upper lobe. Although he had significant residual disease, surgery was contraindicated because of both a recent and an old myocardial infarction. This patient discontinued his drug treatment six weeks after discharge, and six months later was re-admitted to our hospital with catalase-positive, streptomycin-susceptible, INH-resistant organisms in his sputum. This patient was a rapid INH-inactivator, and, in spite

of the high-dosage chemotherapy regimen, the amount of INH given was apparently inadequate as to both dosage and duration. It remains to be seen how many more relapses will occur in the other patients.

Protracted INH therapy of 18 months or more is indicated for the following reasons:

1. The majority of the relapses prior to 1948 occurred within the first year or two after arrest of the disease.[27] 2. A review of the surgical specimens in 100 cases operated upon consecutively at the National Jewish Hospital showed that at least 70% of the specimens contained tubercle bacilli which could be stained but not cultured.

If the initial combined therapy has been adequate, and the sputum converted to negative, INH alone during the period of protracted therapy appears to be sufficient. Generally, the number of viable tubercle bacilli in such cases would be relatively small, and would be existing under anaero-

TABLE 4

Comparison of Similar NJH and VAAF Case Material by Regimens
Chemotherapeutic Results—Bacteriologic Conversion

Regimen	Duration of Therapy		
	1–4 Months	5–8 Months	9–12 Months
NJH[1] SM/INH	(46)* 50%	(46) 100%**	(32) 100%
VA[2] PAS/INH	(94) 39%	(94) 85%**	(58) 91%
VA[3] SM/INH	(123) 40%	(123) 68%**	(88) 75%
VA[4] SM/PAS	(158) 28%	(158) 58%	(95) 64%

[1] SM 15–30 mg./kg./d. for 90 days or more and INH 16 mg./kg./d. for 18 mos.
[2] PAS 12 gm./d. and INH 300 mg./d.
[3] SM 1.0 gm. b.i.wk. and INH 300 mg./d.
[4] SM 1.0 gm. b.i.wk. and PAS 12 gm./d.
* Numbers in ( ) are total cases observed.
** Differences statistically significant: $P < 0.02$.

bic conditions which limit their ability to multiply. Whenever the bacterial population is sufficiently small, it appears likely that adequate single-drug therapy will not be accompanied by the emergence of a drug-resistant population.

SURGERY FOR THE SIGNIFICANT RESIDUAL PULMONARY LESION

Conceding the previously stated effectiveness of adequate combined chemotherapy in controlling the bacillary content of the sputum, our opinion is that surgical intervention should be considered in all significant residual pulmonary lesions. Because drugs effective against dormant tubercle bacilli are lacking, all cavities with inspissated content should, if possible, be resected. Even with effective antimicrobial therapy there is no assurance that these lesions will not continue to serve as a "time bomb" in their capacity to reactivate the infection. A recently completed review of 100 cases operated upon consecutively for pulmonary tuberculosis at the National Jewish Hospital has indicated that surgical intervention might be of value in

cases with radiographic findings of an open cavity or extensive localized nodular disease. In spite of intensive and sustained therapy, one cannot consistently correlate the "activity" by histologic observations of the resected specimens with either the roentgenographic observations or the length of time that the sputum has been converted or has remained negative. Equally disturbing is the already mentioned observation that over 70% of the surgical specimens contained organisms capable of taking the Ziehl-Neelsen stain but were unable to grow by our cultural methods. Will some few of these organisms regain their capacity for reproduction once the antimicrobials have been stopped? Until a long-term, carefully randomized study is performed, resectional surgery should be seriously considered in all cases with significant residual pulmonary lesions, good pulmonary function, and adequate potential life span.

TABLE 5

Therapeutic Response of Cases Drug-Resistant* on Admission to NJH

5–8 Month Evaluation

Total drug-resistant cases on admission			124
Treated and observed 5–8 months			104
Culture remained positive			83
Culture became negative			21
1. With surgery		5	
2. Without surgery		16	
A. Susceptible to one drug	12		
B. Resistant to both drugs	4		
		21	

* Resistant to SM 2.0 mcg/ml. and/or INH 0.2 mcg/ml.

DISCUSSION

Possibly the most crucial period in the treatment of tuberculosis is during the initiation of therapy. If the combined drug regimen or other factors are not adequate, and the patient's organisms become resistant to the antimicrobial agents, the chances of converting the sputum to negative prior to surgery drop rather precipitously. Of 124 drug-resistant patients admitted to the National Jewish Hospital during the period October 1, 1954, through June 5, 1956, only 21 cases became negative despite subsequent intensive therapy: five cases following surgery, and 16 cases following chemotherapy alone. Four of the 16 chemotherapy cases had been excreting organisms resistant to streptomycin and INH, and 12 cases had been excreting organisms susceptible to one of these drugs on admission (table 5).

The implication of this review suggests that failure of chemotherapy of tuberculosis can in part be attributed to the employment of therapeutic measures not specifically designed to take advantage of the maximal potential of the antimicrobial drugs. Although it is our opinion that the therapeutic regimen outlined offers the prospect of permanent inactivation of tuberculosis, further studies on an expanded scale, as well as long-term follow-up, will be necessary before definite conclusions can be reached.

Summary

As a result of the application of newer concepts in the treatment of pulmonary tuberculosis, it appears that we are approaching the point where good therapeutic results are consistently reproducible in patients excreting tubercle bacilli susceptible to the drugs used.

The approach which has been used at the National Jewish Hospital consists of:

1. "Adequate" combined drug therapy: In our experience the most effective therapy has been a combination of streptomycin, 15 to 30 mg./kg./day for 90 days, or more if the culture of the sputum is still positive, and daily high INH dosage for 18 months. Pyridoxine, 50 to 100 mg., is given daily with the INH. We have not as yet encountered a therapeutic failure on this program in patients excreting organisms initially susceptible to the drugs employed. There has been no emergence of resistance prior to conversion to negative.

2. Determination of the dosage of isoniazid by assay methods to insure adequate levels of the antimicrobially active drug in vivo: *There is no standard INH dosage.* Patients vary in their ability to metabolize INH—thus, ideally, prior to therapy with INH all patients should have an assay performed. Approximately 36% of the patients are rapid INH inactivators, and in these, effective INH therapy is achieved only by very high dosage plus the addition of PAS or PABA. The aromatic amines compete with INH for the acetylating mechanism and so permit a higher effective INH serum level. In the absence of definitive INH assay, 8 to 16 mg./kg./day of INH, plus 10 gm. of PAS or PABA, are adequate INH therapy for over 95% of white Americans.

3. Physical activity as a basic principle of treatment: Since INH, streptomycin and PAS are all most effective on multiplying organisms, bed-rest has not been employed unless the patient was toxic. Similarly, collapse therapy (pneumothorax, pneumoperitoneum) was not used in patients who retained drug susceptibility.

4. Surgery for the significant residual pulmonary lesion: Until further knowledge is obtained as to the value of long-term antimicrobial therapy, resectional surgery should seriously be considered in all cases with significant residual pulmonary lesions, good pulmonary function and adequate potential life span, even though the sputum is consistently bacteriologically negative.

Summario in Interlingua

In consequentia del application de plus moderne conceptos in le tractamento de tuberculose pulmonar, il pare que nos es proxime al puncto ubi bon resultatos therapeutic es reproducibile invariabilemente in patientes qui excerne bacillos tuberculotic de typos susceptibile al effecto del drogas usate. Le methodologia utilisate al Hospital Judee National include le sequente aspectos.

1. "Adequate" chimotherapia combinate. In nostre experientia le plus efficace therapia ha essite le combination de streptomycina (15 a 30 mg per kg de peso corporee per die durante 90 dies o plus si le sputo es ancora positive) con alte doses diurne de INH (durante 18 menses). Pyridoxina in doses diurne de 50 a 100 mg es administrate con le INH. Nos ha incontrate nulle malsuccesso therapeutic sub iste regime in patientes qui excerneva organismos de typos initialmente susceptibile al effecto del drogas usate. Ha occurrite nulle caso de disveloppamento de resistentia al drogas ante le conversion al stato negative.

2. Determination del dosage de isoniazido per methodos de essayage pro assecurar adequate nivellos del activitate antimicrobial del droga in vivo. *Il non existe un dosage standard de INH.* Le patientes varia in lor capacitate de metabolisar INH. Ergo, como principio general, essayos debe esser effectuate pro omne patiente individual ante que ille es subjicite al therapia a INH. Circa 36% del patientes es inactivatores rapide, e in istes un efficace therapia a INH es effectuabile solmente per medio de altissime doses supplementate per acido para-aminosalicylic o para-aminobenzoic. Le aminos aromatic es rivales de INH in le mechanismo acetylante e permitte consequentemente un plus alte nivello efficace de INH in le sero. In le absentia de un definitive essayo de INH, 8 a 16 mg de INH per kg de peso corporee per die, supplementate per 10 g de acido para-aminosalicylic o para-aminobenzoic, representa un therapia adequate pro plus que 95% del patientes american blanc.

3. Activitate physic como principio fundamental del tractamento. Proque INH, streptomycina, e acido para-aminosalicylic es omnes le plus efficace in le presentia de organismos in stato de multiplication, allectamento ha non essite empleate excepte quando le patiente esseva toxic. Similemente, therapia collabente (i.e. pneumothorace, pneumoperitoneo) non esseva usate in patientes in qui le susceptibilitate al effecto del drogas esseva intacte.

4. Chirurgia pro significative lesiones pulmonar residue. Usque informationes additional es colligite in re le valor de therapia antimicrobial a longe vista, chirurgia resectional debe esser prendite in serie consideration in omne casos con significative lesiones pulmonar residue si le function pulmonar es bon e si le superviventia probabile es adequate, mesmo in casos in que le sputo es bacteriologicamente negative in omne essayos.

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THE AMBULATORY TREATMENT OF PATIENTS HOSPITALIZED WITH PULMONARY TUBERCULOSIS *

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For the last several years there has been a widespread tendency to liberalize bed-rest requirements in the treatment of patients with pulmonary tuberculosis, increasing ambulation of patients being allowed; indeed, in some treatment centers, nearly complete ambulatory treatment has become the accepted practice. However, there has been no properly controlled study which would compare the results of treatment in patients permitted early ambulation with those in patients on standard bed-rest programs. It is the purpose of this paper to report the results of a study evaluating the need for bed-rest in the treatment of tuberculosis.

Actually, the use of ambulation, exercise or bed-rest in the treatment of tuberculosis has been a point of dissension for nearly a century. In 1869 Brehmer [1] first postulated that the treatment of tuberculosis should be based on open-air management, with carefully administered, graduated exercise. His disciple, Dettwiler, noticed that some patients under exercise seemed to do less well, and he advocated bed-rest in the management of his patients with pulmonary tuberculosis. Since that time the argument has continued, proponents of each school claiming good results for their particular form of rest or exercise. Waring,[2] in the first Amberson lecture, mentioned a paper given at the American Association of Physicians meeting in 1889 in which Bowditch related "the history of my father, cured, as I believe, of severe phthisical symptoms by a journey in an open chaise, and by persistent daily walking of from five to six miles during the rest of his life." Conversely, Brown [3] in 1936 stated that "many, conscientiously and literally, have walked themselves into their graves."

In this country Trudeau initiated sanatorium treatment for tuberculosis, which combined the features of open-air living with bed-rest to a substantial degree, although apparently the program of bed-rest as originally advocated at Trudeau Sanatorium [4] was never the strict bed-rest required in some other institutions. However, through the early part of this century the argument still continued, some competent phthisiologists recommending

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strict bed-rest for their patients and others continuing to advocate graduated exercises. There seemed to be agreement on one general point: as long as patients were symptomatic with an elevation of temperature and toxic symptoms, exercise should be limited, and during the period of gradually increasing exercise, toxic symptoms should be watched for and the degree of exercise limited as necessary to prevent the occurrence of these symptoms. Many articles describing bed-rest actually indicated that it was used only for the early period of several months, or when the patient had toxic symptoms. Amberson [5] in 1937 advocated strict bed-rest for patients with early minimal tuberculosis, most of whom were asymptomatic, and claimed excellent results with this treatment. Bray,[6] however, countered with an article in 1945 stating that, in his experience, early ambulation and graduated exercise in this same type of patient did no harm; and a group of several hundred of his patients did equally well whether treated with ambulation at the beginning, or given a period of bed-rest for about two months early in the course of their treatment. Pratt [7] in 1944 presented a review of the entire problem of bed-rest and ambulation in the treatment of pulmonary tuberculosis, and reviewed the experience since the time of Brehmer. In Boston Pratt introduced a program based on the concept of open-air treatment but associated with relatively strict bed-rest. He had better results than were quoted in other comparable series of cases at that time. After 1920, bed-rest generally was accepted as beneficial in the treatment of tuberculosis, the degree of bed-rest depending upon individual hospital policy and upon the toxic symptoms of the patient. Some advocated very strict bed-rest, with actual immobilization of the chest in plaster casts, with the diseased portion of the lung dependent. Peck,[8] however, presented data clearly demonstrating that this practice of dependent treatment was not always without hazard, as a number of patients developed complete atelectasis of the dependent lung, with toxic symptoms, which cleared only when they were given postural drainage associated with strict bed-rest.

Since the advent of modern chemotherapy the feasibility of the ambulatory treatment of tuberculosis has been reopened. It has been common practice in nearly all hospitals in this country to liberalize the bed-rest restrictions to some degree. It was noted in many institutions that, with drugs in adequate dosage, patients who abused bed-rest privileges did not seem to do a great deal worse than those who were strict or good "bed-resters." It was observed that the morale of the patients was better and the maintenance of discipline somewhat easier with a general relaxation of the rigid rules previously employed in many hospitals.

A study designed to evaluate the necessity for bed-rest in the treatment of tuberculosis was undertaken at Fitzsimons Army Hospital in July, 1954. To accomplish this, patients selected at random were placed in treatment programs either requiring modified bed-rest or allowing early free ambulation.

Methods

Military patients admitted to Fitzsimons Army Hospital with pulmonary tuberculosis were separated into three groups: (1) pleural effusion, (2) minimal pulmonary tuberculosis, and (3) moderate and far advanced pulmonary tuberculosis. None of these patients had received previous courses of chemotherapy for tuberculosis. Patients in each of the three groups were placed in either bed-rest or ambulant programs by random selection based on the last digit of the hospital register number. All patients were initially on modified bed rest on the admission ward for about two weeks before random selection was accomplished. Patients with persistent fever of over 100° F. were not selected for the program. Those patients on the admission ward not becoming afebrile within three weeks were not used in either group.

All patients in this study were treated with streptomycin or streptoduocin, 2 gm. every three days for six months, then 1 gm. every three days for the duration of hospitalization, along with 300 mg. of isoniazid (INH) daily. In August, 1956, the drug treatment was changed to INH, 10 mg./kg. daily, with aminosalicylic acid (PAS), 12 gm. daily for all patients entering either group after that time. However, few patients treated on this newer regimen are included in the present report.

Patients in the bed-rest group were treated with the modified bed-rest program that had been in use at this hospital for several years. Patients initially were kept at fairly strict bed-rest for a period of about three months, during which time they were allowed one bathroom privilege daily and were allowed to eat their meals at their bedside. At the end of three months the patients were advanced in activity and given free bathroom privileges, with about four hours allowed out of bed daily on the treatment ward. When their disease became stabilized, with no x ray change and negative bacteriologic examinations for three months (arrested by NTA standards, 1950),[9] they were allowed out of bed an increasing period of time and were allowed short passes several times a month. Two bed-rest periods of two hours each, morning and afternoon, were strictly enforced. After the disease had reached the inactive stage by NTA standards—six months of stability—only one afternoon rest period of two hours daily was required. Those patients in the ambulatory group were given complete freedom of ambulation from the beginning, but they were allowed to rest in or on their beds if they so desired. They were allowed freedom of the ward and the vicinity outside near the wards. They were allowed to participate in physical therapy and occupational therapy, and to play pool in the ward or croquet or other nonstrenuous sports outdoors in the vicinity of the ward. Although these patients were not prohibited from resting in bed, efforts were made to keep them active. During periods of pleasant weather, which in Denver are quite frequent winter or summer, the patients were outside and out of bed most of the day; however, in periods of inclement weather, and particularly on days when they received streptomycin, there was a tendency for these

patients to lounge around the ward more or less quietly. In addition, in the ambulatory group every encouragement was given to the profitable use of time, and classes were established in the wards to enable these patients to take courses for high school and college credit. During the period of treatment in this ward nearly every patient who so desired or who had the intellectual capacity for it was able to receive credit toward his high school diploma, and in many instances credits for several years of college work. As the program continued this educational feature was made compulsory, and every patient could qualify for a high school diploma before being discharged from the hospital. Power tools were set up in the ward and the patients were allowed free use of these in occupational therapy. Courses in typing, mathematics and military subjects were presented either on the ward or through correspondence courses. These patients, from the beginning, made their own beds and were responsible for the cleanliness of their immediate bedside area. As they progressed through their program of treatment they were responsible for additional work in and around the ward. When they became arrested by NTA standards, 1950, they were classed as noncommunicable and moved to a convalescent ambulatory ward. On this ward they were required to do approximately one-half day of mild to moderate work.

Each patient was followed bacteriologically by culture of sputum or gastric contents or both. These tests were done once every two weeks during the period of hospitalization. X-rays were taken once monthly.

Patients were evaluated by roentgenographic improvement and cavity closure at four months, six months and eight months, and by bacteriologic conversion during this period.

Results

Four general points must be made concerning the results of this study:

1. The patients in the group receiving ambulant treatment were still at rest as compared to their normal physical activity on a duty status in the military service.
2. More than ambulation alone is being evaluated in this program. In general, morale was higher in the ambulant group. These patients also received a great deal of sunlight the year round. By and large, they had more diversional activity and less harassment about ward restrictions.
3. Some patients on bed-rest abused the privileges allowed them, but most accepted bed-rest very well.
4. All of these patients were original-treatment cases.

One hundred eight patients with minimal pulmonary tuberculosis were divided at random into the ambulant and rest program. It was found that it was nearly impossible to make a comparative evaluation of results of treatment in these patients, since they all did well: they became bacteriologically

negative soon after the institution of chemotherapy, with no difference in the two groups. The x-ray improvement in cases with minimal tuberculosis was hard to evaluate, as most had only small areas of lung involved; many had small nodules which showed only a minimal degree of x-ray change. No detailed report will be rendered on these patients. It can be stated that all became negative and progressed satisfactorily to the inactive state. One patient in the bed-rest group showed some x-ray spread of his disease just before making the arrested state, but this was not noted until after his activity was increased. He became bacteriologically positive. The diseased area of his lung was removed surgically a short time after this. The resected specimen was bacteriologically positive on culture. He made a satisfactory recovery after operation. Similarly, in the patients with pleural effusion, no demonstrable difference could be seen in the ambulant and rest groups. Patients did equally well in either group, and again it was not

TABLE 1

Background Data

	Ambulatory	Rest
Total Number of Patients	108	95
	Per Cent	Per Cent
Far advanced	38	22
Moderately advanced	62	78
Negro	13	19
Non-Negro	87	81
40 or Over	11	13
Under 40	89	87
Cavitary	84	73
Noncavitary	16	27
Bilateral	45	55
Unilateral	55	45

profitable to make a more careful evaluation of the data in these patients. Most patients admitted to Fitzsimons with pleural effusion had had the effusion for some period of time before admission. All of the patients with pleural effusion cleared satisfactorily, and all were or became bacteriologically negative and remained so during the entire course of hospitalization. For this reason, data presented in the tables accompanying this article will be only those concerning patients with moderately advanced and far advanced pulmonary disease. It is felt that the only effective means of evaluating the therapeutic results in the patients with minimal pulmonary tuberculosis or pleural effusion will be by relapse rates after a period of years.

Background data on the patients with moderately advanced or far advanced pulmonary tuberculosis are presented in table 1. It should be noted that there was a higher percentage of patients with far advanced cavitary disease in the ambulatory group.

Positive cultures for tubercle bacilli were not a prerequisite for inclusion in the study, but most patients were bacteriologically positive either by means of sputum culture, culture of gastric contents, or by smear or culture of the resected specimen at time of operation. Bacteriologic data on these patients are presented in table 2. Eleven patients of the ambulatory and 17 of the bed-rest group were never positive. None of these 28 patients was operated upon for his disease.

After having been selected for ambulation, two patients on the ambulatory program with moderately advanced or far advanced disease were dropped because of the severity of the disease and poor response to treatment. One patient probably did not meet initial criteria: he was nearly cachectic, with marked weakness, a sallow, nearly jaundiced appearance and with bilateral, far advanced tuberculosis. Even though a diagnosis of carcinoma in addition to tuberculosis was strongly suspected, he was placed on the ambulatory program. At the conclusion of about three months of therapy, because his therapeutic response was poor and early operation was

TABLE 2

Bacteriologic Data

	Ambulatory	Rest
Total number of patients	108	95
Positive on admission	74	62
Positive before admission	16	13
Positive at operation	7	4
Total bacteriologically positive	97 (92%)	78 (82%)
Negative (no operation)	11	17

contemplated for possible carcinoma, he was removed from protocol, and daily streptomycin and higher dosage of INH in addition to PAS were added to his chemotherapy. After this he improved more rapidly and operation was deferred; as improvement continued, the suspicion of malignancy was dropped. The other patient dropped from protocol was an American Indian with far advanced pneumonic disease with cavitation. At the end of two months of treatment he was dropped from protocol and the chemotherapy was adjusted with daily streptomycin and PAS and increased INH dosage. He also showed rapid improvement after change of treatment.

Symptomatic response to treatment has been equal in both groups. All patients have shown a rapid progression to the asymptomatic state under chemotherapy. Hemoptysis of a slight degree occurred in a few patients, on both the ambulatory and the bed-rest programs. Fortunately for the peace of mind of the investigators, the first three cases of hemoptysis occurred in the bed-rest group. Those patients on ambulation who did develop hemoptysis were put to bed for a few days only, and then continued on the program of ambulation. In all patients hemoptysis was of a minor degree and transient, presenting no therapeutic problem.

TABLE 3
Roentgenographic Changes

	120		180		240	
	Amb.	Rest	Amb.	Rest	Amb.	Rest
Moderate or marked improvement	55 (51%)	40 (42%)	61 (62%)	50 (59)%	59 (82%)	48 (75%)
Slight	46	44	31	27	12	14
No change	6	9	2	7	1	2
Worse (noncavitary disease)	0	0	0	0	0	0
Worse (enlarging cavity)	1	2	4	1	0	0
Total evaluated	108	95	98	85	72	64
Cavity closure (nonsurgical)	21 of 90 23%	13 of 70 19%	39 of 82 48%	27 of 61 44%	40 of 58 69%	26 of 43 60%

Data on the evaluation of the chest roentgenograms of the patients with moderate and far advanced tuberculosis are shown in table 3. It would appear that there is only a slight difference in the two groups, but this difference, with regard both to cavity closure and to roentgenographic improvement, favors the ambulant group. It is to be noted that three patients on bed-rest and five patients on ambulation had enlarging cavities at either 120 or 180 days, despite good clearing of their noncavitary disease. As will be mentioned below, three of those on the ambulant program became positive at this time, whereas those on bed-rest did not. In each of these eight patients with enlarging cavities, surgical removal of the cavity was carried out at the six-month point, and they are shown as noncavitary cases at eight months.

Data on the bacteriologic evaluation of patients with moderate and far advanced pulmonary tuberculosis are presented in table 4. It is noted that only 61 of 95 on bed-rest, and 74 of 108 on the ambulatory program were bacteriologically positive by culture on admission to this hospital. There

TABLE 4
Bacteriologic Results

	120		180		240	
	Amb.	Rest	Amb.	Rest	Amb.	Rest
Number positive on admission	74	61	67	54	57	45
Negative at evaluation	74	56	65	51	57	45
Positive at evaluation	0	5	2	3	0	0
Susceptible	—	5	0	2	—	—
Resistant	—	0	2	0	—	—
INH	—	—	2	—	—	—
SM	—	—	0	—	—	—
Susceptibility undetermined	—	—	—	—	—	—

was no difference in the final bacteriologic evaluation in the two groups: all patients were negative after 180 days. Three of the five patients shown as positive at 180 days in both groups had open cavities which were surgically removed at that time, and they were continually bacteriologically negative after that point. Two patients on bed-rest were positive at 180 days, having remained positive since admission. Both of these patients became negative immediately after 180 days without operation, and remained so. One additional patient in the ambulant group became positive at 180 days and was one of those with enlarging cavity mentioned previously. He is not shown in the bacteriologic tables, as he was negative on admission to this hospital. This patient was one of three in the ambulant group who became positive at 180 days with enlarging cavity, with organisms that were susceptible to streptomycin but resistant to INH and catalase-negative.

TABLE 5

Weight Change, Patients with Moderate and Far Advanced Disease

Weight	% Rest	% Ambulatory
−5 to +4	25	25
+5 to +9	46	19
+10 to +15	11	24
+15 to +20	7	21
More than 20	11	11

Data on weight gain in patients with moderate and far advanced tuberculosis were evaluated in a smaller group of patients earlier in this program. The patients on bed-rest showed a greater gain in the five- to nine-pound range, whereas those on the ambulatory program showed a greater gain in the 10- to 14- and the 15- to 20-pound range. These results are shown in table 5.

DISCUSSION

The idea of increased ambulation was not original at this hospital. As mentioned in the introduction, graduated exercise as opposed to bed-rest in the treatment of tuberculosis had been a point of controversy for years before the advent of chemotherapy for tuberculosis. With the use of effective chemotherapy, relaxation of strict bed-rest requirements has been the practice. Several institutions have been using a program of nearly complete ambulation, notably the National Jewish Hospital [10] in Denver and a Veterans Administration Hospital reported by D'Esopo.[11] Although these studies were not carefully controlled with random allocation of patients to either rest or ambulatory groups, the attending physicians felt the patients did just as well as those previously treated on programs requiring stricter bed-rest. In several Veterans Administration neuropsychiatric hospitals,[12] patients with psychiatric disease complicated by pulmonary tuberculosis have been treated with chemotherapy while on complete ambulation. These patients have been locked out of their rooms all day and in some instances

have received therapeutic exercises, these factors being added to enhance the chances of recovery from the psychiatric illness. It has been noted that the results of treatment of tuberculosis in these patients have been good under a program of ambulation more strenuous than that recommended elsewhere. As mentioned previously, none of these programs was well controlled, with a comparable group of patients treated at the same time on a program of bed-rest. For this reason the presently reported study was undertaken at Fitzsimons Army Hospital in 1954. As mentioned previously, the amount of exercise received by many of the patients on our ambulant program was minimal, especially early in the course of treatment, and nearly all of these patients were on a program of rest as compared to their normal activity. It was our intent initially to endeavor to demonstrate only if a program of ad lib ambulation would be harmful; in other words, to let the patient do just what he felt like doing, without needless restrictions and harassment from the ward personnel. It was felt that this should be undertaken first; then, if no harm accrued to those on the more liberal programs, perhaps a new study could be undertaken to determine the effects of increased activity, in the form either of graduated exercise or of actual part-time performance of duty.

There are many advantages in the use of liberalized programs for treatment of tuberculosis if these liberties will not be harmful to the individual. In the hospital these patients require less general nursing care—they are able to aid in caring for themselves. In our hospital they are required to straighten their own rooms and clean their own bedside areas and to make their own beds. These patients are able to pick up their own trays and eat at tables. Educational and recreational programs are easier to administer, as group activities may be established in more central areas. More diversional activities may be planned, including those requiring more exertion and the use of outdoor facilities. All of these factors are a great help in the process of keeping the individual oriented toward self-help and recovery and away from the attitude of dependency and disability previously stressed. This has been particularly valuable and noticeable in the military group we are treating for return to military duty.

While it is urged that all patients with pulmonary tuberculosis be initially hospitalized, it is felt that, particularly in civilian institutions, the period of hospitalization may be drastically shortened for many patients with minimal or even moderate tuberculosis if and when they become bacteriologically negative. The use of ambulatory treatment makes the transition back to normal life easier.

It is felt that the results of this study support the claim that liberalization of bed-rest requirements in patients hospitalized with pulmonary tuberculosis does no harm, certainly in patients with other than far advanced symptomatic disease. In our patients with minimal tuberculosis there has been no significant difference in the results of treatment whether the patient was on rest

or ambulation; actually, as mentioned previously, the only patient who showed any degree of worsening was on the bed-rest program. This patient was also the only one with minimal disease who again became positive after the institution of chemotherapy. He was found to be a rapid inactivator of INH, and serum levels of biologically active INH were below those thought to be clinically effective.

In patients with advanced tuberculosis the question of the advisability of free ambulation has not been completely answered. The results in our study would indicate that liberalization of bed-rest policies would produce little difference in the end results of treatment in these patients. Many patients on ambulation had far advanced disease with bilateral large cavities and did very well under treatment—even a few who were our most arduous exercisers. However, as mentioned under "Results," two patients in the ambulatory program were dropped from the program because of inadequate response to treatment and because of the severity of their disease. In retrospect, these patients were probably too ill to have met the criteria for selection; nevertheless, they were placed in the ambulant program and were left there for two or three months. When placed back on modified bed-rest, with intensification of drug therapy, both patients seemed to show prompt improvement. It is our impression that the improvement was due to the modification in drug therapy, rather than to the change in ambulatory status. However, these cases must still leave some doubt concerning the importance of bed-rest in the early management of the more seriously ill patient. Eight patients in the group studied had enlarging cavities at or before the six-month period, but all of these did well after surgical resection of the cavity, and progressed favorably to the inactive stage after the resection.

As a result of this study we have liberalized the therapeutic program for all patients of this hospital who are not being followed in the randomized study. After the initial period of work-up, all patients are allowed free ambulation around their ward with the exception of two rest periods daily, morning and afternoon. During the morning rest period the patients may work on light occupation therapy, and read or write letters; during the afternoon rest period they are encouraged to sleep or rest quietly but are not required to do so. For patients with more advanced symptomatic disease, or in those who are unable to take drug therapy, bed-rest requirements have been individualized. In this group of patients there has been no untoward incident which would make us regret this use of increased ambulation.

In an individual with minimal or even noncavitary moderately advanced pulmonary tuberculosis it would appear that a program of free ambulation would not be harmful if the individual is receiving adequate chemotherapy. This might imply that some patients could be treated for tuberculosis as outpatients on a program of free ambulation *after* a short initial period of hospitalization to confirm the diagnosis, to get necessary bacteriologic data, to

stabilize the patient on the best drug regimen, and to give him orientation about his disease. Most of these people could return to their normal occupation or, in the case of students, continue their schooling. It has been our experience that practically every patient in this category, even those positive on admission, have become negative and, with one exception, have remained negative throughout their period of treatment. It is not intended to recommend that any patients with active communicable tuberculosis with positive sputum be allowed to roam free in the community, but it is felt that the patient who is persistently negative and is under adequate medical supervision and on chemotherapy might be allowed to rejoin the community and return to work or continue schooling. However, this implies that every patient of this type should be under the constant medical supervision of a competent physician who is well aware of the public health dangers and treatment problems in a patient with tuberculosis.

Finally, this report should not be considered to be a boost for initial outpatient therapy for tuberculosis. All of our patients have been hospitalized at least until reaching the arrested stage of the disease by NTA standards, 1950. It must be reëmphasized that it is our belief that, in general, every patient with pulmonary tuberculosis should receive an initial period of hospitalization.

Summary

1. Data have been presented on the results of treatment in a group of 203 patients with moderately or far advanced pulmonary tuberculosis, selected at random for treatment with either modified bed-rest or free ambulation. All patients received the same regimen of chemotherapy.

2. At the conclusion of eight months of treatment all patients in both groups are bacteriologically negative and have little difference in degree of roentgenographic improvement and cavity closure. Five patients in the ambulatory group and three in the bed-rest group were worse, as measured by enlarging single cavity at either 120 or 180 days. All did well after surgical resection of the open cavity at 180 days.

3. An additional group of 108 cases with minimal pulmonary tuberculosis did well and became bacteriologically negative and inactive, whether in the bed-rest or the ambulatory group.

Summario in Interlingua

Es presentate le resultatos de un studio a selection "al hasardo" comparante in tuberculoticos hospitalisate le effectos de therapia ambulante con le effectos de therapia secundo un programma de allectamento modificate. Patientes militar admittite con tuberculose pulmonar al Hospital Fitzsimons del Armea Statounitese esseva separate in tres gruppos: (1) Casos de effusion pleural, (2) casos de tuberculose pulmonar minimal, e (3) casos de tuberculose pulmonar moderatemente o multo avantiate. Patientes in cata un del tres gruppos esseva placiate in le gruppo a allectamento o in le gruppo del programma ambulante super le base de selection al hasardo. Patientes con febre de persistentemente plus que 100 F esseva excludite.

Le mesmo valeva pro patientes qui non deveniva afebrile intra duo septimanas post lor admission. Omne le patientes includite in le studio esseva tractate con streptomycina in doses de 2 g omne tertie die e con isoniazido in doses de 300 mg per die.

Le patientes del gruppos allectate esseva initialmente restringite a circa tres menses de allectamento satis rigide. Postea illes habeva le privilegio de ir al W.C. e de passar circa quatro horas per die foras del lecto in le vicinitate de lor sala usque illes attingeva le stadio del arresto del morbo. Duo periodos diurne de duo horas de allectamento esseva observate rigidemente usque le morbo attingeva le stadio inactive.

Le patientes del gruppos ambulante habeva complete libertate de action ab le initio. Illes habeva nulle periodos de reposo compulsori, sed on incoragiava les a esser active in le vicinitate de lor salas. Therapia occupational e formas non-fatigante de sport esseva recommendate. Periodos intermittente de labor in nitidar e mantener le sala e su equipamento esseva requirite ab le initio.

Duo centos e tres casos de moderatemente o multo avantiate tuberculose esseva tractate sub le conditiones de (1) allectamento o (2) ambulation libere. Al fin de octo menses de tractamento, omne le patientes in ambe categorias esseva bacteriologicamente negative e habeva disveloppate equal grados de melioration roentgenographic e de clausion de cavitates. In un gruppo additional de 108 patientes con tuberculose pulmonar minimal, omnes progredeva ben e attingeva le stadio inactive del morbo sin reguardo a si illes esseva tractate con allectation o con ambulation libere.

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THE PLACE OF DRUG THERAPY IN THE MANAGEMENT OF UNHOSPITALIZED TUBERCULOSIS PATIENTS*

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The importance of the unhospitalized patient in the over-all tuberculosis picture has been clearly established by the findings of a recent study conducted by the U. S. Public Health Service.[1] This study showed that throughout the country almost half of the significant cases of tuberculosis were at home, the majority with the disease in an advanced, presumably communicable state. This has been the situation in New York City for many years and was the reason for the adoption of a program of drug treatment for unhospitalized patients with tuberculosis by the New York City Health Department in 1953.

This program has as its objective the application of antituberculosis drugs to all unhospitalized patients who present clinical or public health indications for their use. Antimicrobial therapy is provided for three types of patients with active tuberculosis: individuals awaiting admission to a hospital for whom delay is anticipated, those who have left institutions prematurely or relapsed after reaching the stage of arrest, and those who refuse to enter a hospital but do not constitute a serious public health hazard.

Material and Methods

These indications are reflected in the subsequent behavior of the 1,631 patients with active pulmonary tuberculosis who were started on drug treatment in the 23 chest clinics of the New York City Department of Health between July 1, 1953, and June 30, 1954. Of the 793 who failed to complete the prescribed minimal course of 18 months of chemotherapy, 322, or 4%, were admitted to a hospital, usually during the first few months of treatment. Thirty-five per cent lapsed in clinic attendance, and the others were discontinued for a variety of reasons, as shown in table 1.

The age, sex and race distribution of the remaining 831 patients who were observed for two years is given in table 2. A high proportion were white males over 45 years of age. The characteristics of the group at the time antimicrobial therapy in the clinic was started are shown in table 2A.

* From the Symposium on the Treatment of Tuberculosis, presented at the Thirty-eighth Annual Session of The American College of Physicians, Boston, Massachusetts, April 10, 1957.

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TABLE 1

Patients with Active Pulmonary Tuberculosis Started on Drug Therapy in Health Department Clinics during 12 Month Period July 1953–June 1954

Number Removed and Number Remaining for Analysis 24 Months after Start of Treatment

Total started on treatment during twelve month period			1,631
Discontinued before 18 months of Rx (except maximum benefit)		793	
	Number	Per Cent	
Toxicity	34	4	
Admitted to hospitals, etc.	357	45	
Died from tuberculosis	35	4	
Died from other causes	17	2	
Uncooperative	271	35	
Other reasons	79	10	
No report available at 24 months		7	
Total removed			800
Number remaining in study			831

The differences between our material, with its preponderance of advanced cases of long standing, previously treated unsuccessfully, and that of most other reported studies on the results of chemotherapy in tuberculosis are obvious.

Three drug regimens were employed: isoniazid and PAS, isoniazid and streptomycin, and isoniazid-PAS-streptomycin. Approximately 75% of the patients received isoniazid and PAS exclusively. The dose of isoniazid was 5 mg. per kilogram of body weight daily; of streptomycin, 1 gm. twice weekly. Twelve grams of PAS a day, in divided doses, were prescribed. It was not feasible to supervise the taking of oral drugs, to check on the actual intake of PAS, or to make spot determinations of isoniazid concentrations in serum or urine.

Patients were seen in the clinic at least bi-monthly and were x-rayed every two months. Body section radiography was done when indicated. Specimens of sputum were requested each month and examined by culture,

TABLE 2

Characteristics of 831 Patients with Active Pulmonary Tuberculosis at Start of Drug Treatment for Whom a Report Was Available at 24 Months

	Number	Per Cent
Age Groups		
Under 25 years	69	8
25–44	366	44
45 and over	396	48
Sex		
Male	546	66
Female	285	34
Race		
White	405	49
Negro	303	36
Puerto Rican	123	15

gastric lavage or laryngeal swabs being used when the patient was not expectorating. Resistance to streptomycin and isoniazid was determined periodically. Although all patients were advised to secure as much rest as possible, most of them were on almost complete activity and a few were

TABLE 2A

Characteristics of 831 Patients with Active Pulmonary Tuberculosis at Start of Drug Treatment for Whom a Report Was Available at 24 Months

	Number	Per Cent
Stage at Start		
Minimal	105	13
Moderately advanced	435	52
Far advanced	291	35
History of Previous Chemotherapy		
No known previous therapy	328	39
With previous therapy	503	61
Known Duration of Disease		
Less than 1 year	235	28
1–5 years	349	42
Over 5 years	247	30
History of Hospitalization		
Never hospitalized	180	22
Previously hospitalized	640	77
Recently hospitalized	279	34

gainfully employed. In no instance was collapse or excisional therapy applied during the period of clinic observation.

RESULTS

Bacteriologic Results: The status of the sputum of the 831 patients at the start of drug treatment and after 24 months of observation is shown in

TABLE 3

Sputum Status at Start and at 24 Months; 831 Patients with Active Pulmonary Tuberculosis at Start of Treatment

Culture Report at Start of Treatment	Culture Report at 24 Months				
	Total	Positive	Negative	No Report	Per Cent Converted
Positive	537	188	313	36	62
Negative	148	—	134	14	—
No report	146	10	113	23	
Total	831	198	560	73	

table 3. Initially, tubercle bacilli were present in the sputum of four fifths of the patients for whom reports were available. At the end of two years organisms could no longer be recovered on culture from 62% of these patients. In no instance did a patient whose sputum was originally negative

TABLE 4

Change in X-Ray Status 24 Months after Start of Treatment; 831 Patients with Active Pulmonary Tuberculosis at Start of Treatment; by Stage of Disease at Start of Treatment

Change in X-Ray Status	Stage of Disease at Start of Treatment							
	All Stages		Minimal		Moderately Advanced		Far Advanced	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Significant improvement	402	50	66	63	210	50	126	46
No change	308	39	36	35	163	39	109	39
Deterioration	90	11	2	2	46	11	42	15
No x-ray	31		1		16		14	
Total	831		105		435		291	

have a positive culture after 24 months. Reversal of infectiousness occurred in 79% of the patients who had never been given antimicrobial therapy before, but in only 51% of the patients with histories of previous unsuccessful drug treatment.

Roentgenographic Findings: The results in terms of x-ray improvement were much less impressive than was the bacteriologic response after two years of chemotherapy. As indicated in table 4, no change took place in two out of every five patients, and deterioration was noted in 11% of all cases. Improvement was most frequent in those with minimal disease and least frequent in far advanced disease, and it was greater in those who had not received drug treatment previously, irrespective of the stage.

Changes in Activity of Disease: The changes in clinical classification at the end of the 24-month period of observation are shown in table 5. A case was considered to have arrested tuberculosis when roentgenographic stability had been present for at least six months, there was no evidence of cavitation, and tubercle bacilli could not be recovered on culture of sputum or

TABLE 5

Activity of Disease 24 Months after Start of Treatment; Number and Per Cent by Stage of Disease at Start; 831 Patients with Active Pulmonary Tuberculosis at Start of Treatment

Stage at Start of Treatment	Activity after 24 Months							
	Total		Active		Arrested		Arrested with Cavitation	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
All cases	831	100	289	35	455	55	87	10
Minimal	105	100	9	9	94	89	2	2
Moderately advanced	435	100	111	26	281	64	43	10
Far advanced	291	100	169	58	80	28	42	14

gastric contents. Four hundred fifty-five (55%) of the 831 patients whose disease was active before drug therapy in the clinic was started met these criteria at the end of two years. More than three times as many minimal as far advanced cases reached this stage. There were, in addition, 87 patients who satisfied most of the above criteria but continued to show localized rarefaction on their films and who were classified as "arrested with residual cavitation." As might be expected, all but two of these were patients whose original disease was moderately or far advanced in extent. If cases classified as "arrested" and "arrested with residual cavitation" are combined, a total of 542 (65%) of all patients with active tuberculosis before treatment had become inactive after 24 months.

Two other observations of considerable interest were made. One relates to status of the sputum at 12 and 24 months of patients with originally positive sputum, as shown in table 6. Twenty-eight of the 197 patients whose cultures were still positive at the end of 12 months became negative during the subsequent year, a conversion rate of 15%. Simultaneously, 25 (8%) of the 317 negative cases at one year developed positive cultures.

TABLE 6

Sputum Status at 12 Months and at 24 Months; 537 Patients with Positive Culture at Start of Treatment

Status at 12 Months	Total	Status at 24 Months			% Converted Between 12–24 Months
		Positive	Negative	No Report	
Total	537	188	313	36	
Positive	197	157	28	12	15
Negative	317	25	273	19	8
No report	23	6	12	5	

These late changes in bacteriologic status emphasize the necessity for long-term antimicrobial therapy and continued close supervision of nonhospitalized patients.

Data on the development of resistance to isoniazid, determined by the direct method, were collected on the 292 patients whose organisms were sensitive to the drug before treatment. At the end of two years some degree of resistance was noted in 29 of the 51 cases whose sputum was still positive. Most of these were patients who had received drug treatment prior to their inclusion in the program. Tubercle bacilli could be grown on drug-containing media from the sputum of only 12% of all originally positive drug-sensitive patients after 18 months or more of clinic therapy.

DISCUSSION

A program for the drug treatment of a large group of unhospitalized patients with active pulmonary tuberculosis must be evaluated in terms not only of its effect on individual patients but also on the community as a whole.

The conventional yardsticks of sputum conversion, roentgenographic improvement, and changes in clinical classification can be used in the individual, and the accomplishments of the program on this basis have been found to be substantial. A majority of the patients with tubercle bacilli in their sputum before drug treatment became noninfectious following it. Sufficient stability of the disease was reached by the end of 24 months to warrant the classification "arrested" in an even larger percentage of all cases treated. In only 11% of the group were unfavorable x-ray changes noted, and in no instances were tubercle bacilli recovered at the end of two years from patients whose sputum had been negative at the start of drug treatment in the clinic.

Analysis of the results from the public health point of view is more difficult, and requires consideration of such problems as the fate of patients who failed to complete the prescribed course of antimicrobial therapy, the development of resistant strains of organisms and their spread, and the influence of a clinic treatment program on the hospitalization of the tuberculous. An attempt has been made to obtain answers to these questions from the data collected as part of this study.

A total of 1,631 patients were started on drug treatment in the clinics of the New York City Health Department between July 1, 1953, and June 30, 1954; of which 29% received less than four months of therapy, insufficient to justify their consideration in the study. An additional 313 patients were discontinued from clinic supervision six to 18 months after treatment was started, and their status at the time treatment was stopped has been included in the evaluation of clinic antimicrobial therapy from the public health standpoint. This has been done by assuming that those who were still active at the time of discontinuance should be considered as therapeutic failures. On this basis, 51% of all patients given drugs in the clinic could be classified as arrested at the end of two years of observation. When similar criteria are applied, 49% of the originally positive cases had converted their sputum to a noninfectious state in the same period.

Drug resistance is a recognized hazard of continued chemotherapy, whether given in the hospital or clinic. Since more than half of the patients in our program had received antimicrobials previously, it has been very difficult to determine the effect of clinic treatment by itself. Some indication has been provided by analysis of the resistance to isoniazid of tubercle bacilli in the sputum of patients with and without histories of prior drug therapy. Out of 130 previously untreated patients with drug-sensitive organisms in their sputum at the start, only 26 (20%) were bacteriologically positive at the end of two years. Six of these showed some degree of resistance, eight were completely sensitive to isoniazid, and in 12 no sensitivity studies were available. Resistance developed four times as frequently in previously treated individuals. These findings lend no support to the thesis that drug treatment in clinics has been responsible for a significant increase in the amount of drug-resistant tuberculosis in the com-

munity. Recent studies of newly diagnosed cases of tuberculosis in New York City [2, 3] provide further evidence against this assumption.

The most serious criticism of the program advanced was that it would unfavorably affect the hospitalization of patients with active pulmonary tuberculosis. Careful analysis of the records has not borne this out. Eighty per cent of the cases newly diagnosed by Health Department chest clinics are promptly hospitalized now, compared with 64% at the time treatment in the clinics was first begun. The proportion of patients leaving hospitals against medical advice has decreased, and the frequency with which cases return to a hospital for further care has not changed materially. Approximately half of all patients with known active tuberculosis in New York City are segregated in institutions today, a ratio not too different from that of earlier years. These observations have strengthened the writers' conviction that the availability of drug treatment in clinics is a minor factor in the complex problem of the acceptance of hospitalization by the tuberculous.

Summary

1. Antimicrobial therapy with combinations of isoniazid, streptomycin and PAS has been studied over a two-year period in 1,631 patients with active pulmonary tuberculosis started on treatment in the 23 chest clinics of the New York City Department of Health between July 1, 1953, and June 30, 1954.

2. The majority of the 831 patients observed for the full two years were older males with advanced disease of long standing and histories of previous unsuccessful hospital treatment.

3. Sputum conversion occurred in 62% of the patients whose sputum was positive on culture before treatment. Roentgenographic improvement was noted in 50%. The classification of "arrested" was made in 455, and "arrested with residual cavitation" in an additional 87 patients. Sixty-five per cent of all patients had reached a stage of clinical stability by the end of the 24 months.

4. If allowance is made for patients discontinued from supervision after more than six and less than 18 months of treatment, reversal of infectiousness occurred in 49% and arrest of the disease in 51% of all patients treated.

5. Unfavorable x-ray changes took place in 11% of the patients. In no instance were tubercle bacilli recovered at the end of two years from a patient whose sputum before drug treatment was negative.

6. This study has provided no evidence that the provision of drugs by the chest clinics of the New York City Health Department has contributed to the development of resistance to isoniazid in a significant number of patients, or unfavorably affected the acceptance of hospitalization by the tuberculous.

7. It is the firm conviction of the writers that a program of antimicrobial therapy in clinics is an essential supplement to the hospital treatment of patients with active pulmonary tuberculosis.

SUMMARIO IN INTERLINGUA

Un recente studio per le Statounitese Servicio de Sanitate Public ha monstrate que in omne partes del Statos Unite quasi un medietate del significative casos de tuberculose es domiciliari e non hospitalisate. In le majoritate de iste individuos le morbo ha attingite un stato avantiate e presumibilemente communicabile. Un situation de iste genere stimulava le Departimento de Sanitate del Citate de New York a instituer in julio 1953 un programma de chimotherapia pro non-hospitalisate patientes de tuberculose.

Durante le prime anno de iste programma, 1.631 patientes con active tuberculose pulmonar esseva initiate al tractamento per drogas in le 23 clinicas thoracic del Departimento de Sanitate. De illes, 831 remaneva sub observation durante periodos de duo annos o plus. Le majoritate del discontinuatores esseva admittite a hospitales o negligeva lor visitas al clinica durante le prime phases del curso therapeutic. Le majoritate del patientes qui remaneva sub observation esseva masculos de etates plus avantiate con formas progredite del morbo qui habeva essite malade depost longe periodos de tempore e qui habeva historias de non-successo in le tractamento hospitalari. Le regime de drogas usate al clinicas esseva 300 mg de isoniazido e 12 g de acido para-aminosalicylic (PAS) per die.

Conversion de sputo (per cultura) occurreva in 62 pro cento del patientes con sputos positive pro bacillos tubercular ante le tractamento. Melioration roentgenographic esseva notate in 50 pro cento e deterioration roentgenographic in 11 pro cento post duo annos de tractamento. Quatro centos cinquanta-cinque de omne le patientes—i.e. 55 pro cento—satisfaceva le criterios de "arresto" secundo le standards diagnostic formulate in 1950 per le Association National de Tuberculose. Dece pro cento additional habeva culturas negative e stabilitate del constatationes roentgenographic sed non esseva libere de cavitation residue. Iste casos esseva classificate como "arrestate con cavitation." In 15 pro cento del 197 patientes con sputos positive al fin de 12 menses, conversion occurreva in le curso del sequente periodo de 12 menses. Resistentia a isoniazido se constatava post 12 menses de chimotherapia in solmente 12 pro cento del patientes initialmente sensibile a iste droga.

Ab le puncto de vista del sanitate public, le studio del resultatos del programma revela nulle significative effectos adverse. Le frequentia del admission de novemente diagnosticate casos al hospitales, le acceptation del parte del patientes del necessitate de remaner in institutiones, e le incidentia de chimo-resistente casos de tuberculose in le communitate non ha variate appreciabilemente. A judicar secundo le plus rigide criterios de observation consecutori, conversion de sputo esseva presente post duo annos de observation in 49 pro cento de omne le patientes tractate. Arresto del morbo esseva effectuate in 51 pro cento.

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TREATMENT OF TUBERCULOUS MENINGITIS WITH A COMBINATION OF ISONICOTINIC ACID HYDRAZIDES, STREPTOMYCIN AND PARA-AMINOSALICYLIC ACID *

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In a previous paper [1] by one of us (E. A.), the treatment of a series of cases of tuberculous meningitis with isonicotinic acid hydrazides alone was reported. The current paper is based on the use of a combination of isonicotinic acid hydrazides, streptomycin and para-aminosalicylic acid in 41 cases of tuberculous meningitis seen between March 6, 1952, and December 4, 1956.

Clinical Aspects

Table 1 shows the age distribution of the patients in this series. The youngest patient was seven months and the oldest 64 years of age. The wide range in age, with predominance of the younger age groups, is quite evident. The series is comprised of 21 males and 20 females.

Most of the patients presented the typical picture of meningitis. Individual patients showed considerable variation in the severity of the disease, but most appeared critically ill, and four even moribund. The salient signs and symptoms are shown in table 2. These are indicative of diffuse involvement of the central nervous system. Certain symptoms, such as headache, were often difficult to elicit because of the patient's age or mental state. Signs

Table 1

Age Distribution in 41 Cases of Tuberculous Meningitis

Age, Years	No. of Cases
Under 1	6
1 to 10	19
11 to 20	6
21 to 30	5
31 to 40	3
41 to 50	1
Over 50	1
Total	41

* From the Symposium on the Treatment of Tuberculosis, presented at the Thirty-eighth Annual Session of The American College of Physicians, Boston, Massachusetts, April 10, 1957.

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TABLE 2

Salient Signs and Symptoms in 41 Cases of Tuberculous Meningitis

Signs and Symptoms	No. of Cases
Headache	19
Vomiting	26
Fever	41
Convulsions	7
Semistupor or coma	13
Lethargy	17
Irritability	6
Psychosis or delirium	7
Clear sensorium	3
Meningeal irritation	39
Cranial nerve involvement	18
Paresis or paralysis	7
Marked spasticity	6
Sphincteric disturbances	3
Pulmonary involvement	11

of meningeal irritation and a change in sensorium were almost uniformly present. However, a clear mental state was noted in three patients. The cranial nerves most often involved were the oculomotor and facial. Of the seven cases with paralysis, four were instances of hemiparesis. The reflexes were variable, the deep tendon reflexes being more often exaggerated than diminished. Incontinence of urine or feces was observed in three patients. Signs of pulmonary involvement were found in 11 cases. One of the patients was admitted in relapse.

The duration of the meningeal involvement at the time the combined therapy was started varied from two days to two months. As shown in table 3, 22 of the 41 patients were treated within two weeks of the onset of the meningitis. In 16 instances treatment was delayed for three weeks or longer. The three cases of unknown duration included two who developed meningitis while receiving streptomycin and para-aminosalicylic acid for pulmonary tuberculosis, and one in whom the meninges became involved during treatment with isoniazid for a probable tuberculoma of the brain.

LABORATORY STUDIES

Only the pertinent laboratory data in this series will be presented. Table 4 shows the findings in the cerebrospinal fluid. It will be seen that the diag-

TABLE 3

Duration of Meningitis at the Time Combined Therapy Was Started

Duration, Weeks	No. of Cases
Unknown	3
Less than 1	4
1	5
2	13
3	5
4	5
5	3
6 to 8	3
Total	41

nosis was confirmed bacteriologically in 36 cases by finding acid-fast bacilli in the spinal fluid on smear, by recovering *Mycobacterium tuberculosis* from the spinal fluid culture, or by both procedures. In one case, admitted in relapse, the organisms had been isolated from the spinal fluid during the original attack. In another instance, tubercle bacilli were found by gastric

TABLE 4

Spinal Fluid Findings in 41 Cases of Tuberculous Meningitis

Cell Count*	No. of Cases	Protein, mg. %	No. of Cases	Sugar, mg. %	No. of Cases	Chlorides, mg. %	No. of Cases	Organisms by	No. of Cases
Under 100	3	Under 45	2	Under 10	5	Under 600	5	Smear	8
100 to 500	32	45 to 100	11	10 to 40	28	600 to 695	22	Culture	15
501 to 1,000	4	101 to 500	26	41 to 43	5	700 to 800	14	Smear and culture	13
Over 1,000	2	Over 500	2	45 to 73	3				
Total	41		41		41		41		36

* Predominance of mononuclears in 37 cases and of polymorphonuclears in four.

lavage. Two cases were confirmed by the presence of miliary tuberculosis, and one at necropsy. There was also postmortem confirmation of meningeal tuberculosis in five additional cases that had shown the presence of organisms in the spinal fluid. Roentgenologic evidence of pulmonary tuberculosis was found in 27 patients. In one instance, tubercle bacilli were isolated from the sputum, and in another, from the urine. Tests of sensitivity to isoniazid

TABLE 5

Sensitivity of Organisms to Hydrazide and Streptomycin

Hydrazide Sensitivity, μg/ml.	No. of Patients	Streptomycin Sensitivity, μg/ml.	No. of Patients
<0.002	2	0.1	5
0.02	15	1.0	18
0.2	2		
2.0	3		
>20.0	1		
Total	23		23

and streptomycin were made on 23 strains obtained from 19 of the patients. The results of the tests are shown in table 5. The susceptibility of all but one of the tested strains to both drugs is apparent. In the exceptional instance the isolated strain showed resistance to isoniazid. Nonetheless, it should be noted that the patient from whom this strain was isolated re-

covered. The Mantoux test was done in 30 cases and was positive in 28 and negative in two instances.

Treatment

All the patients in this series were treated with the hydrazide drugs and streptomycin, and 26 patients received, in addition, para-aminosalicylic acid. Isoniazid was the hydrazide employed in 37 cases, and iproniazid in the remaining four cases. In two patients who developed meningitis while on streptomycin and para-aminosalicylic acid, hydrazides were added to the regimen, and in the patient in whom meningitis complicated a probable tuberculoma while receiving isoniazid, the dosage of this drug was increased and streptomycin was added.

There was considerable variation in the dosage of these drugs and in the duration of their administration. The dosage of the hydrazides varied from

Table 6

Hydrazide Schedule in 41 Cases of Tuberculous Meningitis

Daily Dose, in Mg.	No. of Cases	Duration of Therapy	No. of Cases
37.5 to 50	5	Less than 1 week	2
75 to 100	11	1 to 4 weeks	5
125 to 250	11	1 to 2 months	4
300 to 400	9	2 to 12 months	6
450 to 550	2	1 to 2 years	17
600 to 800	3	More than 2 years	7
Total	41		41

4 to 18 mg. per kilogram of body weight per day. In most instances a dose of 10 mg. per kilogram was used, and on several occasions doses of 14 to 18 mg. per kilogram were employed. During late convalescence and following discharge from the hospital, the patients were maintained on a dosage of 4 to 6 mg. per kilogram. As shown in table 6, the daily amount of the drug in individual patients varied from 37.5 to 800 mg. On occasion patients required a change in dosage. The medication was used orally in 40 cases, in three of which the initial therapy was administered intramuscularly. In one patient who was in a continuous state of profound stupor, the medication was used parenterally only. Except in the fatal cases, the duration of the hydrazide therapy ranged from four months to four years and four months. In the 12 patients who died, the period of therapy varied from four days to six weeks.

A daily intramuscular dose of 1 gm. of streptomycin was used in 30 cases. Six patients received 2 gm., and five, less than 1 gm. per day. In 10 cases

the dose of the antibiotic subsequently was changed to 1 gm. two or three times a week. In addition to the intramuscular medication, two patients received several intrathecal injections of 50 to 100 mg. of the drug. The duration of the streptomycin therapy varied from three days to 17 months, but it ranged between two months and one year in the majority of the cases. The daily dosage of para-aminosalicylic acid ranged between 2 and 16 gm. and was between 6 and 12 gm. in the majority of the cases. This medicament was used orally only. Except in the fatal cases, therapy with para-aminosalicylic acid was continued for periods ranging from one month to two years.

In addition to the specific treatment, one patient with marked muscular spasticity received corticotropin, 50 mg. daily for one month, and another patient with signs of arachnoiditis and a cauda equina syndrome was treated with prednisone, 20 mg. per day for two and one-half months. Various antibiotics and sulfonamides were used for intercurrent infections, and gavage was employed for feeding and administering drugs to patients who were in a state of stupor.

Most of the patients were treated on an ambulatory basis as soon as the meningitis appeared to be under satisfactory control. Following discharge from the hospital, they were maintained on hydrazides, alone or in combination with para-aminosalicylic acid.

Results

Initial Improvement: The initial changes indicative of clinical improvement that followed the combined therapy became apparent at varying intervals. Remission of the fever was attained in from one to 10 weeks. Improvement in the mental state and recession of the signs of meningeal irritation were noted generally in from two to eight weeks. In one patient the nuchal rigidity persisted for more than six months. A state of well-being and gain in weight became manifest in the majority of the cases in from one to three months. These changes were not noted in the patients who died shortly after admission.

Clinical Course during Treatment: The clinical course in this series is summarized in table 7. It will be seen that after the initial favorable response, improvement usually progressed slowly and was interrupted in many instances by occasional febrile episodes, and at times by adverse developments. The latter included spasticity, evidence of arachnoiditis with paraplegia, hemiparesis, impairment of vision, deafness, sphincteric disturbances, decubitus ulcers and bladder calculi. Most of these complications cleared up gradually, but some persisted. In some cases improvement was relatively rapid, progressive and uncomplicated. The clinical course in the fatal cases was short and very severe. However, three of these showed temporary improvement which was followed by deterioration. Of particular interest is the fact that such extraneous conditions as pregnancy, operative inter-

vention and intercurrent infections were well tolerated during the clinical course.

Spinal Fluid Changes during Treatment: With the institution of the combined therapy, early disappearance of the organisms from the spinal fluid was noted in all but two instances. The exceptions were two fatal cases in which tubercle bacilli persisted for about two weeks, up to the time of death. Generally, the return of the other abnormalities of the spinal fluid to normal was delayed for weeks or months. The pleocytosis persisted for periods of from three weeks to five months, revealing many fluctuations, and in some instances it rose to more than 1,000 cells per cubic millimeter. The elevated protein levels persisted for a similar range of time, occasionally showing marked quantitative increases. For instance, protein levels ranging from 1,000 to 4,900 mg. per 100 c.c. were noted in seven cases. There were striking fluctuations in the sugar content. The final return to normal generally occurred in from one to five months. In three cases the sugar became normal in from one to two weeks, and in one it remained abnormal for nearly a year. In three cases the sugar content was normal on admission but declined subsequent to the institution of therapy in two instances, and in the third remained normal up to the time of death.

TABLE 7

Clinical Course during Treatment in 41 Cases of Tuberculous Meningitis

Nature of Course	No. of Cases
Moribund, with rapid death	4
Progressive deterioration	8
Relatively rapid, uncomplicated improvement	9
Slow improvement, with febrile episodes and adverse developments (spasticity, paresis, impairment of vision, deafness, sphincteric disturbances, decubitus ulcers, bladder calculi)	20
Extraneous conditions (respiratory infections, measles, varicella, rickettsial pox, pregnancy, lithotomy)	10

Serum and Spinal Fluid Drug Levels during Treatment: From one to eight determinations of the concentration of isoniazid and streptomycin in the serum were made in each of six patients, and from one to 15 determinations in the spinal fluid were made in each of 20 patients. In the serum isoniazid levels varied from 1 to 8 μg and streptomycin levels from 1 to 32 μg per milliliter. In the spinal fluid the isoniazid levels ranged between 0.5 and 16, and the streptomycin levels between 0.5 and 8 μg per milliliter. Since the levels were not correlated with the time of administration of the drugs and since there was no correlation between the serum and spinal fluid levels, the determinations were not too informative. However, they did indicate that both drugs were present in the blood and spinal fluid in significant amounts.

Outcome: In this series of 41 cases there were 29 recoveries and 12 deaths. Four of the patients who died were moribund on admission and received the combined therapy for very short periods (from four to 10 days).

In three of the patients with fatal termination there was evidence of a temporary response to the medication. As shown in table 8, the survivors have been observed for periods ranging from four months to four and one-half years, and at present most of them are in good general physical condition and have normal mentality. The lungs cleared in 18 out of 20 patients with pulmonary involvement.

Complications: Marked muscular spasticity and mental retardation were observed in three of these patients, in one of whom there was also optic atrophy. One patient had spastic contractures of the legs and optic atrophy, but a normal mental state. Five other patients with lesser degrees of muscle spasm and paresis have responded to physiotherapy and have improved steadily. The remarkable improvement in the patient with arachnoiditis and the cauda equina syndrome has been of special interest.

Toxic Reactions: Untoward effects were encountered in 10 cases. Tingling of the face and extremities occurred in one patient, and was attributed to isoniazid. A maculopapular skin eruption was observed in four

TABLE 8

Observed Period of Survival in 29 Recovered Cases of Tuberculous Meningitis

Observed Period of Survival	No. of Cases
4 months to 1 year	2
1 to 2 years	7
2 to 3 years	9
3 to 4 years	6
4 to 4½ years	5
Total	29

patients, in one of whom it appeared to be due to streptomycin, and in another to para-aminosalicylic acid. In the remaining two cases the cause of the rash could not be determined. Deafness, presumably due to streptomycin, developed in one patient. Two instances of nausea and vomiting and one of diarrhea were ascribed to para-aminosalicylic acid. In another case, vomiting was attributed to isoniazid. All these reactions cleared up. Except for transient positive cephalin flocculation tests in three patients, the laboratory investigations showed little evidence of drug toxicity.

Relapses: Two of the patients in this series relapsed. In one of these the recrudescence occurred two months subsequent to discontinuation of medication, following a five months' course of treatment. The second patient relapsed one month after the discontinuance of the drugs, which had been used for only six weeks. These patients responded satisfactorily to retreatment with combined therapy.

Postmortem Findings: Necropsies were performed in six of the fatal cases. In five of these there was generalized miliary tuberculosis, complicated by tuberculous meningitis, with considerable clearing of the meningeal involvement in one instance. In the sixth case there was tuberculous

meningitis, associated with extensive cerebral infarction due to obliterative arteritis.

Discussion

It is clear from this study that the combined therapy was effective in the treatment of the majority of the cases of tuberculous meningitis. In general, the patients fall into three groups, namely, one with complete recovery, another with recovery associated with sequelae, and a third with failure of response. Undoubtedly, the disease was more severe in the patients who failed to respond, but this study does not permit a definite delineation of the factors that influenced the outcome. Although the early institution of appropriate chemotherapy is a principle of paramount importance, it did not necessarily obtain in several instances. In the light of subsequent experience, it is our impression that some of the cases early in the series were probably treated inadequately.

With respect to the fatal cases, it has already been mentioned that four were moribund on admission and died within a few days. In another fatal case the necropsy showed, in addition to the meningitis, an extensive area of infarction of the brain. Obviously, one could not expect these five patients to have benefited from any medication. In three of the patients with fatal termination there was temporary improvement. At necropsy these cases revealed the presence of miliary and meningeal tuberculosis, and in one there was considerable clearing of the meningitis. It is difficult to understand why the initial improvement in these cases did not progress, especially since patients with miliary tuberculosis as a rule respond admirably to isoniazid, alone or in combination with other drugs. This has been noted by King,[2] Pfuetze and Desautels,[3] Wier [4] and others. In another fatal case the patient probably had a large tuberculoma, and the meningitis was a terminal event. In the remaining three fatalities it is even more difficult to explain the failure of response. It is noteworthy that all the deaths occurred within six weeks following the institution of the combined therapy.

As previously mentioned, all but one of the tested strains of tubercle bacilli, including strains from six of the fatal cases, were sensitive to both isoniazid and streptomycin. The exception was a strain that was susceptible to streptomycin but resistant to isoniazid. The patient in this case recovered and has been maintained on isoniazid alone for more than two years. Since streptomycin was used for only five months in this case, it would seem that isoniazid has played an effective role in the arrest of the patient's infection. It is conceivable that the disease in this instance was of a less progressive nature, since it has been shown by several investigators [5, 6, 7, 8, 9] that tubercle bacilli resistant to isoniazid often lose their virulence for guinea pigs and have limited pathogenicity for man. However, there is no doubt that bacilli resistant to isoniazid have the capacity to produce disease in man, as pointed out by Cohen and Glinsky [10] and Rist.[11] Undoubtedly,

the problem of resistance to isoniazid requires further investigation. In the present state of knowledge it is not possible to correlate strictly drug susceptibility of the organisms with the clinical response of patients.

The occurrence in four of the cases of serious sequelae, such as marked muscular spasticity, mental retardation and blindness, is quite disturbing. What bearing, if any, delay in therapy had on the development of these complications is difficult to say. Although in two of these patients treatment was delayed for five weeks and two months, respectively, therapy was instituted on the second day of illness in the third case, and in the fourth patient the disease developed while he was on a combination of streptomycin and para-aminosalicylic acid. In regard to the blindness, which was due in each instance to optic atrophy, it was pointed out by one of us (E. A.) in a previous study [1] that the complication was probably the result of pressure by the tuberculous exudate and of some of the effects of the healing process. The value of hormones in the prevention or alleviation of neurologic complications, as recommended by several workers,[12, 13, 14, 15, 16, 17] merits further study. It was difficult to appraise the value of the hormone therapy employed in two of the cases in this group.

The relatively low incidence of untoward effects in this series is rather impressive. Particularly striking is the fact that toxicity attributable to the hydrazides was encountered in only two instances. Since there appears to be a direct relationship between the dosage of isoniazid and the frequency and severity of side-effects, as stressed by Selikoff and his associates,[18] and by Coates et al.,[19] the reduced incidence of toxic reactions in this group may be attributed to the use of the hydrazides in moderate doses. On the other hand, some workers, notably Debre and Brissaud,[20] apparently attach little if any significance to the toxic potentialities of isoniazid and favor the use of large doses of the drug. These investigators routinely have employed doses of 20 to 30 and even 40 mg. per kilogram. Further studies obviously are needed to clarify the relationship of the dosage of isoniazid to the incidence of side-effects. The transient positive cephalin flocculation tests are difficult to appraise. In general, it may be noted that the toxic side-effects were transitory and rarely interfered with the therapeutic regimen.

The high rate of relapse in patients with tuberculous meningitis who were treated with streptomycin alone is well known. The introduction of hydrazides has reduced considerably the incidence of recrudescence. It is essential, however, to continue this medication for a period sufficiently long to control the meningeal infection. Obviously, in the two instances of relapse in this series, the therapy was discontinued prematurely. The precise duration of treatment required to insure arrest of the infection is at present unknown. It is important to note that there was no recrudescence in any of the patients in this series while they were receiving hydrazides, alone or in combination with other antituberculous drugs.

With regard to the prevention of meningeal involvement, it has often

been stated that no case of tuberculous meningitis has developed in patients who were treated with isoniazid, alone or in combination with other drugs. Although this may hold true generally, it is not entirely borne out by our experience, or by that of Lincoln and Lythcott.[21] Tuberculous meningitis developed in one of our patients who had been receiving isoniazid for a probable tuberculoma. It is possible that in this case the nature of the underlying disease interfered with the success of the medication, since, as was pointed out by Vandiviere and his associates,[22] tubercle bacilli in circumscribed lesions exist at a low level of metabolic activity and frequently are unaffected by drugs. In the case reported by Lincoln and Lythcott, meningitis developed after a course of eight months of isoniazid therapy for pulmonary tuberculosis. In this instance, however, there appears to be some uncertainty regarding the continuity of treatment.

It may be of interest to compare the results obtained in this series with those of a previous study,[1] in which the patients were treated with hydrazides alone. In the earlier series there were 10 cases, with seven recoveries and three deaths. One of the fatal cases was moribund on admission and died within four days after the institution of therapy. The survivors have been observed for nearly five years, and all but one are in excellent condition, physically and mentally. The exception is a patient with incomplete optic atrophy, who has regained a fair degree of vision. Although it is difficult to compare two groups that are numerically disproportionate, nonetheless it may be noted that the patients who were treated with hydrazides alone fared as well as did the patients in the current series. In the light of our experience, and in view of the high degree of effectiveness of the hydrazides in miliary tuberculosis, it is apparent that these drugs constitute the main therapeutic agents in some if not all forms of tuberculous infection, and it seems to us that the use of hydrazides alone in the treatment of tuberculous meningitis merits further clinical trial.

In addition to the question of the choice of regimen in the therapy of tuberculous meningitis, there are many other pertinent problems that require further study. These relate to drug resistance, dosage of isoniazid, duration of treatment and the value of hormones and other measures in the prevention of serious sequelae.

Summary

Forty-one patients with tuberculous meningitis were treated with a combination of isonicotinic acid hydrazides and streptomycin, and in many instances with para-aminosalicylic acid as well. The diagnosis was confirmed bacteriologically in 36 cases by finding acid-fast bacilli in the spinal fluid on smear, by recovering *M. tuberculosis* from the spinal fluid culture, or by both procedures. In one case in relapse, the organisms had been isolated during the original attack. In another, tubercle bacilli were found by gastric lavage. Two cases were confirmed by the presence of miliary tuberculosis, and one case at necropsy. Roentgenologic evidence of pul-

monary tuberculosis was found in 27 patients. In most instances the dose of the hydrazides was 10 mg. per kilogram of body weight, of the streptomycin 1 gm., and of the para-aminosalicylic acid 6 to 12 gm. per day. Of the 41 patients, 29 recovered and 12 died. The survivors have been observed for periods ranging from four months to four and one-half years, and at present most of them are in good general physical condition and have normal mentality.

In this series there were relatively few toxic reactions, particularly as a result of the hydrazide therapy. Serious neurologic residua were encountered in only four cases. Relapse occurred in two patients who responded satisfactorily to retreatment with combined medication. Several important problems, particularly those pertaining to the choice of regimen, duration of treatment and prevention of sequelae, require further investigation.

SUMMARIO IN INTERLINGUA

Quaranta-un patientes con meningitis tuberculotic esseva tractate con un combination de hydrazidos de acido isonicotinic e streptomycina. Vinti-sex de illes recipeva etiam acido para-aminosalicylic. Le patientes exhibiva le symptomas typic de meningitis. Le majoritate de illes esseva apparentemente multo malade, e certes esseva mesmo moribunde. In 36 casos, le diagnose esseva confirmate bacteriologicamente per le detection de bacillos acido-resistente in frottis de fluido spinal, per le obtention de *Mycobacterium tuberculosis* ab culturas de fluido spinal, o per medio de ambe iste methodos. In un caso, que se trovava in stato de recidiva, le organismo habeva essite isolate durante le attacca initial. In un altere caso, bacillos tubercular esseva trovate per lavage gastric. Duo casos esseva confirmate per le presentia de tuberculose miliar. In un caso, le confirmation se obteneva al necropsia. Signos roentgenologic de tuberculose pulmonar esseva trovate in 27 casos.

Le dosage del drogas e le duration del curso therapeutic variava considerabilemente. In le majoritate del casos le dose del hydrazidos esseva 10 mg per kg de peso corporee, illo de streptomycina esseva 1 g, e illo de acido para-aminosalicylic 6 a 12 g per die. Post le subjugation initial del meningitis, multes del patientes esseva tractate secundo un regime con ambulation. Ex le 41 patientes, 29 se restabliva e 12 moriva. In general, le melioration progredeva lentemente in le patientes qui succedeva a restablir se, e frequentemente illo esseva interrumpite per episodios de febrilitate e a vices per disveloppamentos adverse. Le superviventes ha essite tenite sub observation ulterior durante periodos de inter quatro menses e quatro annos e medie, e al tempore presente le majoritate de illes se trova in bon stato physic general con mentalitates normal.

In le presente serie, il habeva relativemente pauc reactiones toxic, specialmente como resultato del uso de hydrazidos. Serie residuos neurologic esseva incontrate in solmente quatro casos. Recidivas occurreva in duo patientes qui respondeva satisfactorimente al retractamento per medication combinate. Nulle recrudescentias esseva incontrate in ulle del patientes durante que illes recipeva hydrazidos, tanto in isolation como etiam in combination con altere drogas antituberculotic. Le comparation del resultatos obtenite in le presente serie con le resultatos observate in un previe studio in que hydrazidos esseva usate sol revela nulle appreciabile differentia. In le lumine de nostre experientia e viste le alte grado de efficacia del hydrazidos in casos de tuberculose miliar, il es clar que iste drogas representa le major agente therapeutic in multe, si non in omne formas de infection tuberculotic. Nos opina que le uso de

hydrazidos sin supplementation per altere drogas in le therapia de meningitis tuberculotic merita essayos clinic additional.

Plure importante problemas, specialmente le problemas del selection del regime, del duration del curso therapeutic, e del prevention de sequellas, require investigationes additional.

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TREATMENT FAILURES IN TUBERCULOSIS *

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ANTITUBERCULOUS drugs have given the treatment and control of tuberculosis a new look, but the glamour of combating a highly fatal disease is a thing of the past—rather, must we look upon our problem as the much less spectacular and more arduous prevention of a chronic relapsing infectious disease. The plunging death rate is only a red herring in the current epidemiology of tuberculosis. The decline in mortality is a modest expression of success in the conquest of tuberculosis over the years, with due credit to workers in the field, but with more than a slight compliment to Mother Nature and Darwinian forces.

Ten years or so ago, one quarter (24%) of our tuberculous patients were carried out the back door of our sanatoria in pine boxes for their last ride. But times have changed, and today they walk out the front door on their own two feet, homeward bound, looking well and healthy. It would thus appear that the death rate is no longer a reflection of the tuberculosis problem. Instead of counting gravestones, we must look into our homes and family circles, into our community centers and institutions where old cases abound and new cases are found.

The New York State Tuberculosis Hospital report through 1955 [1] presents some data of more than minor interest along these lines.

Several observations are clear from these facts. First, the total number of patients discharged from the sanatoria back to our homes and communities is large and appears much more important than the Sanatorium deaths. Second, the total bed occupancy per year is thus more significant than the number of empty beds in any census count. Third, in New York State just under 40% of discharged patients are returned to their homes still active, with positive sputum or gastric contents, representing for the most part the recalcitrant patients who refuse treatment.

The 61% of inactive cases at the time of discharge remain potential relapses today, just as in the past. In spite of modern drugs and surgery, sufficient time has not yet elapsed to determine how many of these inactive cases will break down in the future. Before the days of chemotherapy, approximately 80% of the relapses in well-treated cases of tuberculosis occurred within five years of the completion of therapy according to Mitchell at Trudeau and DeFriez at the Channing Home in Boston. Today the slowly mounting relapse rate has reached only 10% at the end of the same

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TABLE 1

New York State Hospitals

Condition of Patients on Discharge

Year	Number Discharges	Per Cent Dead	Per Cent Alive
1945	400	25.0	75.0
1950	764	18.0	82.0
1955	1,021	8.0	92.0

TABLE 2

New York State Hospitals

Activity Status of Patients on Discharge

Year	Number Discharged	Alive	
		% Inactive	% Active
1945	301	45	55
1950	624	55	45
1955	936	61	39

five-year period, following the most careful plan of drugs and surgery. We can only speculate as to the future of the drug-treated patients.

In 1955 the United States Public Health Service [2] made an extraordinarily important nation-wide study to seek the facts concerning the nonhospitalized tuberculosis patient. It was a search for definitive data concerning the treatment and follow-up of individuals diagnosed and reported as tuberculous. The work is familiar to some of you. Therefore, I will utilize only a few of its factual contributions with which to refresh your memory and to use as a springboard for future discussion.

This extraordinarily stimulating and definitive study has proved most revealing to everyone concerned and furnishes a clear mandate pointing out the directions in which our antituberculous energies may be expanded. Its figures reflect a national trend, and they do more than suggest that the care of the tuberculous patient is slipping out of the hands of the tuberculosis specialist in the ivory towers of our sanatoria into those of the family doctor and the clinic physicians.

Whether this trend is good or bad, whether we like it or not, these are

TABLE 3

Summary of Findings of U. S. Public Health Service Survey

1. Roughly one-half (45%) of active cases of tuberculosis were at home.
2. Of these 87% had advanced tuberculosis.
3. The bacteriologic status of the sputum was unknown in one-half the cases and was positive in one-half of those examined.
4. Of the active cases 40% were receiving neither antituberculous drugs nor rest on this so-called home cure.
5. One quarter (24%) of these active nonhospitalized patients had no known medical supervision.

the facts. Personally, I believe the trend is not beneficial unless patients at home can receive care equivalent to the best sanatorium treatment available. Acute, toxic, infectious tuberculosis should have sanatorium care or its equivalent. If this U. S. Public Health Service study reflects a continuing trend in the management of tuberculosis and the results of treatment of the nonhospitalized patient continue to look equally poor, then the over-all care of this group—nearly one-half of all active tuberculosis patients—is indeed a source of failure of treatment.

It may be of interest to this group that in examining young doctors for their American Boards of Internal Medicine this last week, those who were questioned on this subject were unaware of these trends in the distribution of active cases of tuberculosis, and were remarkably naive about what constitutes good modern therapy in this disease.

Why do we worry about therapeutic treatment failures rather than think about our successes? The answer is self-evident: the propagation of tuberculosis still comes from the infectious relapsing case, and adequate care is essential to the prevention and cure of this disease.

There are other causes for the failure of treatment that deserve our concern, for it is not the 80 to 85% of individuals who recover without complications on conventional or unconventional regimens of rest and chemotherapy and surgery who require our most scrupulous attention—it is the 15 to 20% of patients who deteriorate or fail to improve on treatment or relapse later. These are the sources of contagion, the origins of new cases. Only a few of these will I choose for expansion:

Causes for Failure of Treatment

1. Inadequate supervision of the non-hospitalized patient.
2. Constitutional susceptibility to tuberculosis (familial trend).
3. Inadequate rest.
4. Refusal to take treatment—(recalcitrant patient).
5. Drug sensitivities and intolerance.
6. Resistant organisms.
7. Inadequate drugs or insufficient duration of administration.
8. Inactivation (acetylation, etc.) of INH and PAS.
9. Inappropriate surgery—too early or too late.
10. Non-tuberculous acid-fast rods mistaken for tuberculosis—*Nocardia,* atypical, chromogens, etc.
11. Wrong diagnosis—cancer, pneumoconiosis, nontuberculous granulomata, etc.

1. *Inadequate supervision of the tuberculous patient who is not hospitalized* for one reason or another has been discussed. It would seem reasonable, however, that this problem be met by our medical schools through undergraduate education and by postgraduate educational courses.

3. *Bed rest and its needs in tuberculosis* have been based on empirical ideas over the years, impressions based on experience without the benefit of science. Laennec recommended the seashore in the middle of the nineteenth century. Deitweiller in 1876 was the first to recommend strict bed rest. A few years later Patterson recommended hard labor for the cure of tuberculosis.

Trudeau then produced the Adirondack Mountain rest cure, along with a touch of fishing and hunting. Boston's Bowditch sent his patients on long horseback and buggy rides throughout New England until Dr. Joseph Pratt in 1911 set the pattern for long continued strict bed rest. Bowditch vilified Pratt in public for his conservatism, but Amberson and others up to 1950 observed and recommended the benefits of rest in tuberculosis. It is hard to believe that these wise and critical clinicians misconstrued the facts.

Dr. Kass, today, has led us into the realms of imaginative chemotherapy without bed-rest, but without much evidence to *prove* that ambulation and exercise are beneficial in the chemotherapy of tuberculosis or that bed-rest in any form can be ignored. His theory is attractive, his early results look good bacteriologically, but they need the test of time before wide adoption.

Dr. Robins has shown the results of chemotherapy alone without much other control of activities, as has Stocklen in Cleveland, who had to cope with an emergency shortage of beds. About 50% of Robins' cases did well on this routine, but the other 50% did poorly, a figure that is really not as good as in the days before chemotherapy when patients were treated with bed-rest only. Thus in advanced disease chemotherapy without rest does not appear to be sufficient treatment for tuberculosis.

Dr. Wier in his excellent controlled study of the comparative effects of bed-rest versus no bed-rest has shown that individuals ambulated as in-patients at Fitzsimons General Hospital did no worse than those on 20 hours a day of bed-rest. But if I recall the American Soldier accurately, in war or peace, in any general hospital, he spends as much of his day as possible flat on his back or close to it. I would therefore, ask Dr. Wier if his group, hospitalized on Command order, may not be a highly selected one, living under conditions so protected as hardly to be compared with the vigorous life led by Dr. Robins' patients, or the less protected life of those cared for at home.

Somewhere between these facts and fancies is an optimum of combined rest and chemotherapy. Time may solve this concept of how much rest is needed with chemotherapy, but for the moment, a reasonable compromise may prove feasible. For the very minimal, nontoxic, asymptomatic lesion, a normal academic life or its equivalent with 10 to 12 hours "off the feet," and *adequate* chemotherapy for one to two years will be good treatment in most cases. These patients must, however, be watched every two to three months by x-ray and with examination of the gastric contents, for any deterioration in their course.

For sick, febrile patients with fresh lesions whether minimal or advanced but of uncertain course, we physicians in Boston still individualize, and bed rest of 20 hours a day, more or less, is still recommended for this active group until good progress has been established by a stable x-ray and clinical course. For those being cared for at home this is a realistic program.

7. *The effects of chemotherapy in the prevention of therapeutic failures* has been discussed in a highly significant way by Dr. Kass. His invasion of the realms of theory touches on what may eventually be common practice. His studies, however, represent results based upon most complicated and expert bacteriologic work which we in this part of the country are not prepared to duplicate. I have personally reviewed these studies by Middlebrook at the National Jewish Hospital as well as those by Dr. Morse at the Fitzsimons General Hospital, and I have been greatly impressed by their work.

Their observations of the destruction or acetylation of INH by the body, their rapid cultural methods with demonstration of sensitivity on primary inoculation, and their analysis of total bacterial populations concerning the proportion of resistant and sensitive organisms are most fundamental, and demand exacting bacteriologic technic. Until one is prepared to do this work, however, or has it available, he is ill prepared to adopt their complicated drug regimens.

I believe, therefore, we would do well to stick to more standard regimens of drugs until the test of time has warranted a change. In the large studies of the Veterans Administration—Army—Navy—Air Force, isoniazid in doses of not less than 300 mg. a day, with PAS 10 to 12 gm. daily, has proved to be the best combination of drugs for the conversion of sputum, closure of cavities and clearing of roentgenographic changes. Streptomycin 1 gm. twice weekly, or daily in severe cases, with PAS runs a close second in its effectiveness. Isoniazid with streptomycin, individually the two best drugs, have no apparent additive effect and in the long run have not so far proved clinically superior in pulmonary tuberculosis. Proof of the destruction of INH within the body, however, makes larger doses—up to 600 mg. or more a day, with pyridoxin 50 mg. to protect from neuropathies —advisable in those with advanced disease, in our experience.

Bacteriologically, however, indications are appearing that isoniazid and streptomycin together have a usefulness in therapeutic failures or their prevention. Triple drug treatment of pulmonary tuberculosis still verges on the controversial, but it has not been shown to be superior in any definitive way. In extrapulmonary tuberculosis triple drug therapy—streptomycin, isoniazid and PAS—has been thought in the past to be the most effective combination, and it still is, generally, but newer studies are pointing to an equal effectiveness of only two drugs.

In these regimens of drugs two things remain important, that primary uninterrupted combined therapy once started should be continued without

interruption for not less than one year in the most minimal case and that it should be continued for from two to three years in the more advanced cases.

Time does not permit elaboration of other more highly experimental combinations of drugs using pyrazinamide, cycloserine and the newest but most uncertain streptovaracin.

9. *Surgery* will not be considered here except to urge the consideration of combined medical and surgical opinion, to avoid being too early or too late, with too little or too much of the mechanical aids that surgery may contribute to the case of tuberculosis that does not do well on drugs and modified rest.

Summarizing. Let there be no complacency concerning the eradication of tuberculosis just because of the falling death rate. Not until the best of long-term chemotherapy, judicious surgery and appropriate rest have found a way to master the problem of the "treatment failure" can we even hope for final success. Those of us who are engrossed in this problem, talk too much to our own professional confreres about these matters with which they are already familiar. We do not talk enough concerning these things to the people or to the family doctors who are most vitally affected. This subject of the tuberculous population of every community, whether composed of new or old, active or inactive cases, has become a top priority for our public relations and for treatment and control. This "new look" of tuberculosis must be woven into our undergraduate and postgraduate medical teaching. It must be presented to our lay groups in a manner sufficiently seductive to secure their action and support as well as their interest.

If these trends toward the care of the patient outside the hospital are not accompanied by greatly improved management in the future, then our "treatment failures" will assume a greater importance.

Summario in Interlingua

Le subjugation de tuberculose ha cessate esser le problema de manipular un morbo eminentemente mortal. Il se tracta hic in nostre tempore plus tosto de un multo minus dramatic morbo con chronicitate e recidivas, e le marcate descendita del mortalitate non reflecte le natura del problema e non es un indice del incidentia de tuberculose in le communitate.

In le Stato de New York le anno 1955 videva tres e medie vices le numero de dimissiones hospitalari in casos de tuberculose que le anno 1945. Quaranta pro cento del patientes dimittite habeva ancora tuberculose active. Il es iste patientes qui retorna in nostre communitates con tuberculose in forma active o in forma inactive qui representa le ver e le potential problemas in le subjugation de iste morbo.

In le anno 1955, le Statounitese Servicio de Sanitate Public, sub le direction de Dr. Bloomquist, executava un enquete relative al non-hospitalisate patiente de tuberculose. Resultava le sequente constatationes:

1. Quasi un medietate (45%) del casos de tuberculose active se trovava in domicilios private.
2. Octanta-septe pro cento de iste casos habeva tuberculose de forma avantiate.
3. Le stato bacteriologic del sputo esseva incognoscite in un medietate del casos. Illo se monstrava positive in un medietate del casos examinate.

4. Quaranta pro cento del casos active non recipeva drogas antituberculotic e non sequeva un regime de reposo in iste si-appellate cura domiciliari.

5. Un quarto (24%) del active casos domiciliate habeva nulle apparente surveliantia medical.

Si iste mediocre standard continua determinar le regime therapeutic del futuro, il es a expectar que "cura al domicilio" se revela como causa non solmente de missuccessos therapeutic sed etiam de numerose nove casos de tuberculose.

Altere causas de missuccesso therapeutic debe esser restudiate. Depost le medio del seculo XIX, opiniones contradictori in re le rolo de allectation in le tractamento de tuberculose ha nunquam cessate tormentar le medico e le patiente. In nostre dies le situation non es differente. Dr. Robins ha monstrate que chimotherapia sin ulle programma de reposo o modification del activitate lassa multo a desirar in le resultatos final. Post duo annos, 50 pro cento de su patientes habeva ancora tuberculose active.

Dr. Kass ha recommendate le abandono de allectation sin provas convincente pro le soliditate de su theorias. Su programma utilisa un complexe regime de chimotherapia que es bon in le theoria sed que require ancora le prova del tempore. Usque le resultatos es confirmate, chimotherapias del typo conventional representa un plus practic methodologia therapeutic. Inadequate doses de drogas administrate durante inadequate periodos de tempore es le principal causa de missuccesso drogal. Le destruction o le acetylation del hydrazidos de acido isonicotinic intra le corpore non es estimate per plus que un parve numero de laboratorios, e il es possibile que isto es un causa de missuccesso drogal que pote esser vincite solmente per grande doses del agente chimic. Pyridoxina deberea semper administrar se con hydrazido pro prevenir su effectos neurotoxic. Acido para-aminosalicylic es apparentemente capace a prevenir le destruction de hydrazido per le corpore, e il pare que le combination de iste duo drogas remane le plus recommendabile. Doses de 1 g de streptomycina duo vices per septimana es possibilemente insufficiente, e in "missuccessos therapeutic" e in casos avantiate 1 g de streptomycina per die in combination con hydrazido o acido para-aminosalicylic es forsan requirite. Nonobstante, duo punctos remane importante: (1) Sufficiente quantitates de droga debe esser administrate durante sufficiente periodos de tempore. (2) Post que le combinate therapia primari es instituite, illo debe esser continuate durante al minus un anno in le casos le plus minimal e durante inter duo e tres annos in casos plus avantiate.

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CASE REPORTS

PHEOCHROMOCYTOMA AND PREGNANCY *

By Irving L. Stutz, M.D., F.A.C.P., Sidney A. Rosenburg, M.D., Harold M. Cohen, M.D., Robert Chamovitz, M.D., and Irwin Bogarad, M.D., *Pittsburgh, Pennsylvania*

The diagnosis of pheochromocytoma is being made with greater frequency since more reliable tests for its recognition have come into more or less widespread use. It is not, however, encountered frequently. A review of 2,720 autopsies done at the Montefiore Hospital since it was opened in July, 1929, failed to reveal a single instance of pheochromocytoma. Pheochromocytoma complicated by pregnancy remains a very uncommon situation. Keir [1] recently reported the successful removal of a pheochromocytoma from a 32 year old white woman in the third month of pregnancy, with cure of the patient's symptoms and survival of the fetus. Numerous authors have mentioned the similarity of preeclampsia or toxemia of pregnancy to pheochromocytoma. Hypertension during pregnancy poses a particularly difficult differential diagnostic problem, with essential hypertension, renal disease or toxemia of pregnancy to be considered along with less frequent causes. The period at which the hypertension has its onset may be of some value from the standpoint of differential diagnosis; it is generally thought that hypertension seen in the first trimester suggests preëxisting renal disease or essential hypertension, and that hypertension occurring in the last trimester probably represents a toxemia of pregnancy.[2] Measures which may be necessary for diagnosis should of course include a complete history of the patient, plus a physical, chest x-ray, electrocardiogram, urinalysis (including a urine culture), urea nitrogen, phenolsulfonphthalein, Fishberg concentration, pyelogram and the Regitine test.

Peelen [3] recently reported a case of pheochromocytoma associated with pregnancy and reviewed the literature. He stated that there were 19 previous cases of simultaneous pheochromocytoma and pregnancy. Including his case, the 20 patients had had a total of 30 pregnancies. As pointed out by him, the mortality rate is high (nine deaths, a 45% mortality rate). The danger attending pheochromocytoma in pregnancy is attested to by the occurrence of eight of these deaths within 72 hours after delivery. Wallace and McCrary,[4] in reporting an instance of pheochromocytoma in April, 1955, stated that their case represented the thirteenth instance of pheochromocytoma associated with pregnancy. Maloney [5] reported a case of pheochromocytoma with pregnancy in which he stated that his case was believed to be the first reported in which the

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diagnosis was made ante partum. His patient was delivered by cesarean section, followed by adrenalectomy, with survival of both mother and child.

The case which we are reporting would seem to be the twenty-first medically recorded instance of pheochromocytoma and pregnancy.

Case Report

The patient was a 28 year old Negro female, gravida II, para I, who was admitted to the Montefiore Hospital on August 10, 1955, because of profuse vaginal bleeding during the seventh month of pregnancy.

The patient had apparently always enjoyed good health, and she resolutely denied knowledge of any previous cardiovascular-renal disease. In the summer of 1954, on seeking medical attention because of headaches, dizziness and weight loss, she was found to be free of hypertension, and the physical examination did not disclose anything of note.[6] She then remained well until she was first seen in the Out Patient Obstetrical Clinic in March, 1955, for an early pregnancy. Her blood pressure on this occasion was 160/90 mm. of Hg. On three subsequent visits between then and the time of her admission in August her blood pressures and urinalyses were reported as normal. On direct questioning the patient did admit to having excessive perspiration with some heat intolerance within the last few months.

Her previous obstetrical history revealed that she had had what was considered a normal pregnancy and delivered in 1952. The past medical history revealed "hepatitis" in 1949. Her only surgery consisted of a tonsillectomy in 1941. She had experienced only the usual childhood illnesses.

At the time of her admission in August, in the seventh month of her pregnancy, there was profuse vaginal bleeding; the fetus was viable, the uterus irritable, and the cervix undilated. She was treated with bed-rest, intravenous fluid, sedation and blood replacement.

At this time her initial blood pressure was 150/180 mm. of Hg, but during the next three days it varied between 120/80 and 190/110 mm. of Hg. The laboratory studies revealed a hemoglobin of 9.1 gm.; white blood cells, 19,900, with 83% neutrophils and 17% lymphocytes. Urinalysis showed a trace of albumin, with 6 to 7 white blood cells and some granular casts. Serologic tests for syphilis were negative; nonprotein nitrogen, 25 mg.; creatinine, 1.2 mg.; uric acid, 14 mg.%. Chest x-ray was reported as normal.

On August 13, medical consultation was requested because of the presence of the hypertension. Examination revealed a pleasant, well developed, well nourished, pregnant female in no acute distress. Funduscopic examination showed a minimal amount of vascular spasm. Examination of the heart and lungs was not remarkable. No edema was present, and the blood pressure at this time was 190/110 mm. of Hg.

The patient was continued on bed-rest and sedatives, in the hope of getting a larger baby. On August 19, because of persistent and progressively increasing blood pressure (230/130 mm. of Hg), she was started on a low salt diet, reserpine and a veratrum preparation (Veriloid). The effect on the hypertension was nil; the blood pressure continued to be unstable, varying from 130/100 to 230/130 mm. of Hg.

A number of catheterized urine specimens continued to reveal slight albuminuria, with white blood cells and casts in the sediment. The best concentration during a Mosenthal test was 1.016, and the phenolsulfonphthalein was 37% after one hour.

The patient's course was discussed at a combined obstetrical and medical staff conference; the prevailing opinion was that the patient presented an instance of atypical preëclampsia, although she had no edema or abdominal pain, and very little nausea and vomiting. The frequency with which pheochromocytoma masquerades as eclampsia or toxemia has been commented upon by numerous authors.[7, 8, 5] The

suspicion of toxemia would be strengthened with the occurrence of an elevated blood uric acid such as this patient presented.[9]

While the obstetrical department was considering cesarean section upon the patient, she went into spontaneous labor on September 9, delivering a premature but viable male baby. The placenta remained attached and had to be removed manually, which involved slight difficulty. Blood pressure prior to delivery was 160/110 mm. of Hg, and immediately following delivery rose to 270/130 mm. of Hg. Within five minutes it had dropped to 140/120 mm. of Hg, at which time the patient's pulse remained at 160. At this time she was cold and clammy, and perspired profusely. An electrocardiogram at this time revealed a sinus tachycardia. Several large blood clots were expressed from the vagina. The patient was treated for shock with intravenous fluid, blood, sedatives, narcotics and chlorpromazine. During all this time her blood pressure ranged from 100/90 to 180/120 mm. of Hg. Our impression of a possible pheochromocytoma took stronger hold at this time, and within a few days confirmatory tests for the presence of a tumor were instituted. By the third day post partum the pressure had dropped to 140/90 mm. of Hg. The uric acid fell to

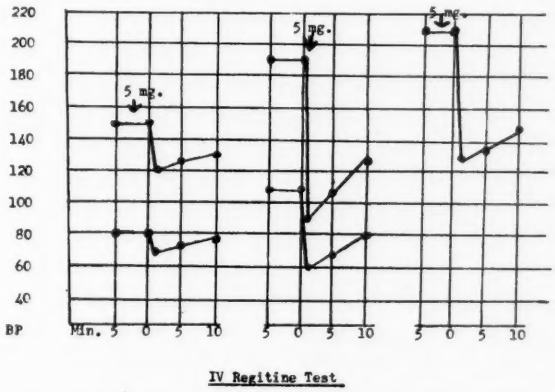

FIG. 1. Characteristic response to Regitine intravenously.

8.6 mg., and the nonprotein nitrogen remained at the upper limits of normal. However, the patient continued to present a leukocytosis, with a white blood count of 19,800, and 75 neutrophils and 25 lymphocytes. On the following day the white count was 36,200, with 94% neutrophils and 6% lymphocytes.

Between September 9 and 15 three intravenous Regitine tests were done, two being strongly positive (figure 1). The basal metabolic rate, done on two occasions, was reported as plus 29 and plus 16. However, an intravenous glucose tolerance test presented a normal curve. A number of fasting blood sugars were within normal limits; nevertheless, on three occasions urinalyses revealed a mild to moderate glycosuria.

It was noted on several different occasions that, upon assuming the erect position, the patient developed marked changes in pulse and blood pressure, with marked postural hypotension and tachycardia. Thus, on September 16, her supine blood pressure was 210/160 mm. of Hg and pulse was 88. Immediately upon standing, her blood pressure fell to 126/100 mm. of Hg and her pulse increased to 136. This response of the blood pressure and heart rate with changes in position in patients with pheochromocytoma has been commented upon frequently by observers.[10, 11, 12] On

several occasions, too, the patient had cardiac arrhythmias, and this finding has also been frequently noted in patients with pheochromocytoma.[13] Arrhythmias reported include multifocal ventricular extra beats, runs of nodal tachycardia with a wandering pacemaker, sino-atrial block, T-wave changes and, at times, peaked P-wave changes. On many occasions when the patient's pressure was elevated she complained of headache and perspired profusely. On several such occasions the radial and dorsal pedal pulses became much less evident and the extremities became quite cold.

An intramuscular Regitine test gave positive results (figure 2); a histamine test was attempted with an initial pressure of 150/100 mm. of Hg; immediately following the administration of .05 mg. of histamine base, the pressure fell to 120/80 mm. of Hg. Unfortunately, within a few minutes the patient developed a severe headache that prevented the taking of any additional blood pressures (figure 2). A cold pressor test was positive, in contrast to what might be expected in the individual with pheochromocytoma (figure 3), and the sodium amytal test yielded a paradoxic rise instead of fall, but this has been reported by some observers.[11] I^{131} studies were interpreted as showing a euthyroid state.

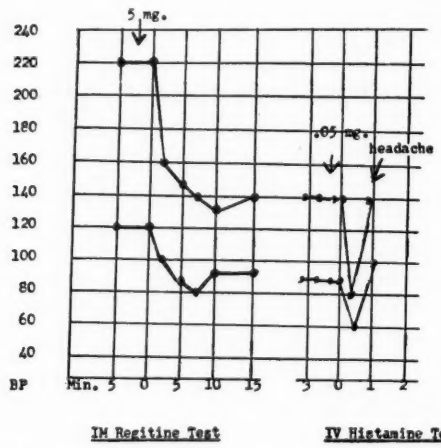

FIG. 2. A. Similar response to intramuscular Regitine. B. Immediate drop following intravenous histamine; agonizing headache made continued observation of its effect on patient impossible.

An intravenous pyelogram was reported as normal, but the right kidney was said to be somewhat lower than expected. Presacral air studies revealed normal bilateral renal shadows, with slight ptosis on the right, and also what was thought to be a normal left adrenal. No masses were visualized, nor was the right adrenal.

On September 5 the patient began to have headaches and noticed blurred vision. Funduscopic examination at this time revealed grade IV hypertensive retinopathy, with papilledema of the right eye and grade III changes in the left eye; the latter progressed to grade IV changes with papilledema within a few days.

A 24-hour urine specimen sent to Dr. Goldenberg[14] in New York City was reported as having 1,805 mg. norepinephrine and 216 mg. epinephrine. He was convinced at this point that the patient had a functioning chromaffin tissue tumor.

On October 7 the patient was started on intramuscular Regitine, in the hope of

preventing any further vascular damage by decreasing the blood pressure. At about this time her pressure was approximately 220/130 mm. of Hg. The following day cortisone, 100 mg. per day, was started for preoperative preparation.

On October 10, under Pentothal and nitrous oxide anesthesia through a right flank incision, the right renal area and retroperitoneal space were explored. No abnormal masses were encountered, and there was no increase in the blood pressure with manipulation in this region. However, it appeared as though the adrenal might be somewhat enlarged, and it was removed, since it was felt at this time that if a tumor was not found on further exploration, a total or subtotal adrenalectomy might have effected some improvement, as has been reported frequently in the recent literature. The blood pressure ranged between 120/80 and 220/140 mm. of Hg, with a pulse rate of 110 to 160. During the operative procedure the patient received an intravenous Regitine drip, 25 mg. in 500 c.c. of solution, and 10 mg. of hydrocortisone during a period of an hour, also by intravenous drip. Biopsy of the right kidney was reported as minimal arteriolar thickening with cloudy swelling of the glomerulotubular cells. The adrenal was microscopically normal.

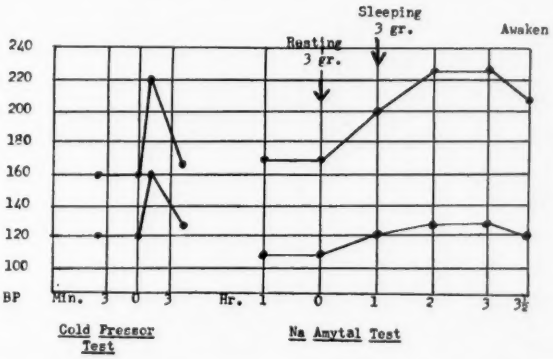

FIG. 3. Paradoxic response to both cold pressor test and sodium amytal.

The postoperative course was marked by episodes of sudden increase of blood pressure, with readings frequently exceeding 160/130 mm. of Hg. When the blood pressure rose over 170/130 the patient was placed on intravenous Regitine drip, with good results. These paroxysmal attacks were accompanied by marked perspiration and vascular spasm, and were present for as long as a three-day period. Removal of the right adrenal gland had had no effect on the over-all hypertension. The patient again responded to the stress by a marked leukocytosis of 23,250, with 82% neutrophils.

Oral Regitine, 50 mg., was given over a three-day period, with no noticeable effect on the blood pressure. On October 19, with the same preoperative schedule of Regitine and steroids, the patient was again explored surgically through a left ventral incision, and a 3.5 by 2.5 cm. mass was felt in the left adrenal gland (figures 5 and 6). No masses were palpable along the aorta. During induction of anesthesia (figure 4) the blood pressure rose to 240/150 mm. of Hg, and the patient was again started on intravenous Regitine drip. With manipulation of the left renal area, and especially the tumor itself, the blood pressure rose to 220/155 and 240/170 mm. of Hg, respectively, and the Regitine drip was speeded up, with good hypotensive effect. With the ligation of the tumor's blood supply the blood pressure rapidly fell, and when it

reached 90/50 mm. of Hg, intravenous Levophed was started and the blood pressure maintained at 140/90 mm. of Hg.

Approximately one third of the left adrenal was left intact, with a good blood supply. Three portions of the removed adrenal tissue were replaced in the abdominal wall in an attempt to obtain adequate adrenal function, since the other adrenal had been sacrificed.

Postoperatively the patient was maintained on Levophed for five hours, and then was put on 10 mg. of neosynephrine/1000 c.c. of glucose to maintain a blood pressure of 140/90 mm. of Hg. Both drugs worked equally well, and by the twenty-eighth hour postoperatively the patient was able to maintain her blood pressure at 130/90

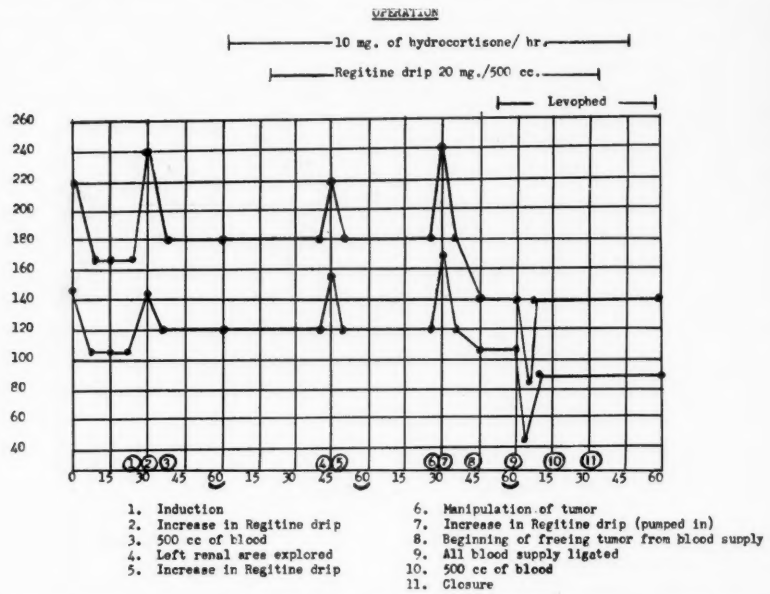

FIG. 4. Effect of anesthesia, manipulation and exploration of tumor area on blood pressure. Control by Regitine.

mm. of Hg without aid from pressor drugs. She received, in addition, parenterally and later orally, steroids (cortisone) in daily decreasing dosage; these were discontinued 10 days postoperatively. The blood pressure ranged between 120/80 to 150/90 mm. of Hg while she remained in the hospital, but the other symptoms and signs of pheochromocytoma were not present.

The pathologic report of the tumor was pheochromocytoma without malignant characteristics. It was analyzed by Dr. M. Goldenberg [14] and found to contain norepinephrine, 1.69 mg. per gram of tumor tissue, and epinephrine, .25 mg. per gram of tissue. The normal adrenal gland contains 1.0 mg. pressor substance per gram of gland.[15, 16]

Whereas a preoperative electrocardiogram had shown nonspecific ST-T wave changes, the postoperative tracing was reported as consistent with coronary insufficiency. The postoperative uric acid was 4.1 mg., the basal metabolic rate was minus 2%, and the white count, which had always shown a marked leukocytosis with other

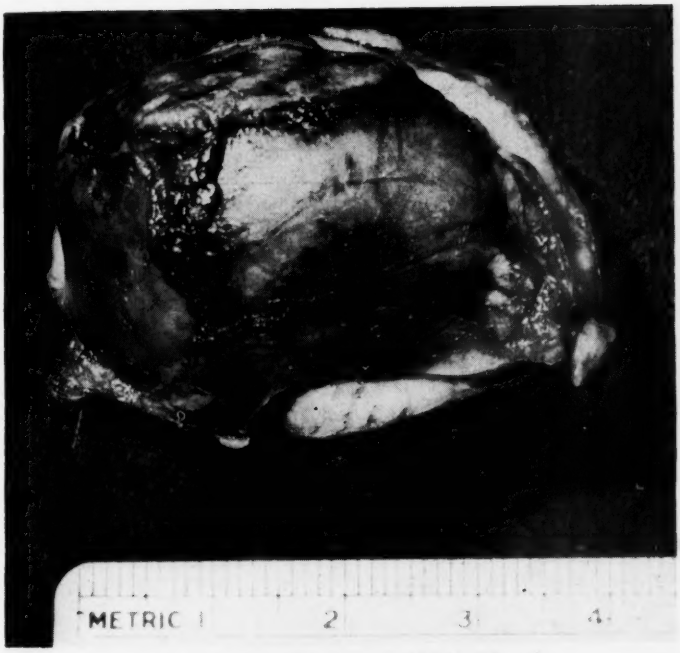

FIG. 5. Photograph of tumor (3.5 by 2.5 cm.).

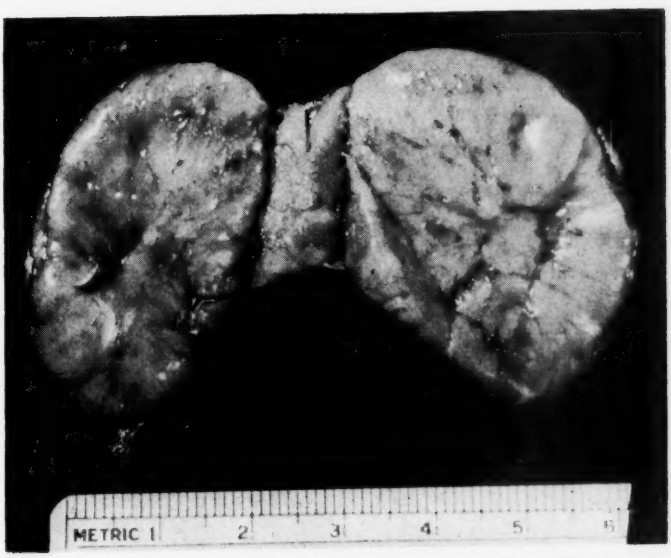

FIG. 6. Cross section of tumor. Microscopic sections did not disclose any malignant changes.

TABLE 1

Showing Normal Range of Electrolytes, Even Though Patient Now Has Only Portion of One Adrenal Gland

	Eosinophil Count		Urinary Sodium/ 24 hrs.	Circulating Corticoids	
	8 a.m.	4 p.m.		8 p.m.	4 p.m.
Control day	209	—	130 mg.	288	148
First day	176	99	308 mg.	118	198
Second day	204	215	226 mg.	138	248

ACTH I.V. Drip—25 Units.

stresses, was only 13,000 after the tumor was removed. The albuminuria diminished to a very faint trace.

Because of the possibility of hypo-adrenalism, the patient was followed with daily blood sugars, weight, sodium, potassium, chlorine and urinary sodium excretions. All these remained within the normal range. In the hope of encouraging some adrenal hypertrophy, the patient was given an intravenous ACTH drip, 25 mg., lasting six to eight hours, on three separate days. Eosinophil, urinary sodium excretions, and circulating corticoids were done by Dr. Joseph Warren,[17] of the Montefiore Hospital Research Laboratory, in order to evaluate adrenal cortical function (table 1). The first morning the corticoid level was elevated over that which would be expected, which may have been due to a laboratory error, or possibly to unmetabolized cortisone given prior to the test.

Since discharge from the hospital the patient has been followed in the Out Patient Clinic. She has remained largely asymptomatic and has gained 11 pounds. She is able to do her own housework without fatigue. Blood sugars, complete blood counts, electrolytes and electrocardiograms are all within normal limits. The urine still occasionally shows a trace of albumin, with an occasional white cell. The blood pressure usually is in the neighborhood of 130/90, although it has been as low as 120/80 and has risen to as high as 160/110 mm. of Hg. The retinal findings have reverted to the point of only minimal vascular changes.

TABLE 2

Comparison of Patient's Findings with Those Reported by Smithwick in His Series

Symptoms and Signs	Our Patient	11 Cases Reported by Smithwick	107 Cases Collected by Smithwick
Excessive sweating	Yes	90%	52%
Vasomotor phenomena	Yes	90%	47%
Elevated temperature	No	78%	70%
Normal cold pressor (no response)	No	73%	63%
Fasting blood sugar of 120 mg./100 c.c. or more	No	64%	61%
BMR of plus 20% or more	Yes	60%	57%
Postural tachycardia	Yes	55%	—
Postural hypotension	Yes	44%	50%
Glycosuria	Yes	36%	50%
Paroxysmal attacks	Yes*	36%	75%

* Patient maintained a persistent hypertension with several episodes of sudden marked increase in blood pressure.

Discussion

The patient exhibited many of the symptoms and signs suggestive of pheochromocytoma. A comparison of this patient's findings with those reported by Dr. Smithwick [10] is presented in table 2. This patient's response to the sodium amytal test was similar to that reported by others,[11, 18, 19] that is, a marked increase in blood pressure while asleep. This is thought to rule out psychogenic factors of essential hypertension, but actually may be explained as being due to coincidental outpouring of epinephrine.

The patient also consistently responded to varied stresses, such as vaginal bleeding, delivery and surgery, with a marked leukocytosis. No attempt was made to determine whether the patient had an increased tolerance to epinephrine, as has been reported by Maycock and Rose [20] in patients with functioning disorders of the adrenal medulla. The white count did not return to normal after the stress period. After the second surgical procedure and removal of the tumor the leukocytosis did not develop. We are unable to state whether this represents another aspect of the clinical picture of this condition, or just happens to be an individual patient's response to bleeding and/or stress. We have been able to find in the literature only two cases with a leukocytosis of over 15,000, one occurring in a patient with a salmonella abscess in an asymptomatic pheochromocytoma found post mortem,[21] the other in a case of pheochromocytoma diagnosed post mortem, again without signs of infection or bleeding.[22] Of course, it has been shown that an adrenalin drip will cause an increase in blood volume and number of circulating leukocytes.[23] It would appear that, if this were responsible for leukocytosis, it would be seen regularly in patients with pheochromocytoma, which is not the case.

In a period of less than two weeks this patient received 220 mg. of Regitine parenterally and 300 mg. orally. We observed none of the toxic symptoms and signs described by Trapold et al.[24] In our opinion, the drug maintained its hypotensive effect in this two-week period and did not interfere with the use of hypertensive drugs (Levophed) after the removal of the tumor.

The diagnosis of pheochromocytoma was entertained as an initial impression during the first few days the patient was in the hospital. Diagnostic procedures were not done at this time because of the patient's condition, a result of the vaginal bleeding, since it was felt that the procedures would lessen the chance of getting a larger baby.[25] In retrospect, it would appear that this was an error in judgment. The patient had an extremely stormy course following spontaneous delivery, and the outcome appeared in doubt because of her dire condition. It is now well established that patients with pheochromocytoma do not tolerate any stressful situation, and many fatalities from "surgical shock" with even minor operations occur in patients with pheochromocytoma, particularly in those in whom the condition is unsuspected.[25, 26, 27]

Paulshock and Miller [28] recently reported a fatality occurring in an elderly patient with hypertension shortly after surgery, emphasizing again the fact that pheochromocytoma may occur even in elderly patients, and that failure to be aware of its presence may be disastrous. Even in patients undergoing surgery for a suspected pheochromocytoma, the mortality ranges from 15 to 30%, although recently it has improved considerably in this respect.[3, 21] It has been demonstrated recently in animals that an intravenous adrenalin drip will initially

result in an increase in blood pressure, but will later cause a decrease, and shock and death will appear after the drip is stopped.[22] Loss of the intravascular fluid, resulting in hemoconcentration, is thought to be the mechanism, and the process has been shown to be reversible by the giving of blood and intravenous fluid. This same sequence of events has been observed in patients with prolonged paroxysmal attacks of pheochromocytoma, and is possibly the mechanism that results in the surgical shock and death of these patients.[19] From our experience with this patient, it is our belief that when the diagnosis of pheochromocytoma is suspected it should be investigated immediately before any other procedures are done.

Summary

1. An additional instance of pheochromocytoma complicated by pregnancy is reported. This represents the third case in the literature which has been diagnosed ante partum with successful removal of the tumor.

2. Difficulties of diagnosis have been commented upon, with emphasis on the fact that toxemia rather than pheochromocytoma is most likely to be suspected.

3. Though pheochromocytoma complicated by pregnancy is not a common occurrence, the importance of diagnosis is stressed, with a special comment on the seriousness to the mother and child. Confirming the more recent literature, we feel that the employment of urinary screening tests for pressor amines, plus the use of Regitine, provides the best means for diagnosis at present.

Summario in Interlingua

Le tableau clinic de hypernephrinemia in association con pheochromocytoma es cognoscite depost plus que 30 annos. (Su description original esseva publicate per Labbé et al.) In despecto de isto, multe casos de functionante tumores a cellulas chromaffin escappa indubitosemente al observation, viste le facto que le majoritate del discopertas de tal tumores es facite durante necropsias. Quando le pheochromocytoma es associate con pregnantia, su non-recognition deveni ancora plus probabile—excepte in casos de altissime indices de suspicion—proque le resultante hypertension es facilemente interpretate como effecto de toxemia de pregnantia, hypertension essential, o un pre-existente morbo renal. Isto es illustrate per le caso de pheochromocytoma occurrente como complication de pregnantia, que es hic reportate per le autores. Al tempore de su declaration, le condition esseva reguardate como pregnantia con toxemia. Durante que toxemia de pregnantia representa un satis grave periculo pro le feto e le matre, le non-recognition de pheochromocytoma, si illo existe sub iste conditiones, curre un ancora plus serie risco de ducer a consequentias disastrose. Viste le alte fidelitate e efficacia del nunc disponibile methodos pro le diagnose de pheochromocytoma—specialmente le methodos del differentiation chimic del urina per que le demonstration de augmentos del catechol-aminos succede quasi invariabilemente—le recognition de pheochromocytoma es possibile con alte grados de certitude, mesmo in caso de pregnantia. Isto es specialmente importante proque il ha essite monstrate que, mesmo durante le intervallos normotensive de hypertension paroxysmal, le essayage del urina forni importantissime datos positive. Del altere latere, le autores debe reportar que Dr. M. Goldenberg, qui possede ric experientias in iste aspecto del problema, mentionava in un recente communication private le caso de un patiente in qui normal aminos pressori del urina esseva trovate durante un phase normotensive e in qui, nonobstante, le presentia de pheochromocytoma esseva ulti-

memente provate. Si le suspicion de pheochromocytoma persiste sub iste conditiones, le induction de un stato de hypertension—per exemplo per medio de histamina—va provider le base pro resolver le question.

Le autores crede que le presente caso es le tertie de pheochromocytoma con pregnantia in que le diagnose esseva establite ante parto, sequite per le successose ablation del tumor e un cura subsequente del hypertension.

Si tosto que le diagnose de pheochromocytoma es establite, mesuras pro le ablation del tumor debe esser prendite, in cooperation intime del internista, del chirurgo, e del anesthesiologo.

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CARCINOMA OF THE STOMACH IN ASSOCIATION WITH HIATUS HERNIA *

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Esophageal hiatus hernia is now a frequent finding during gastrointestinal roentgen examinations. The incidence has been variously estimated as between 2 and 3.5%. These figures are conservative; a hiatus hernia can be demonstrated during barium meal examination in approximately 10% of all patients. Although there have been occasional statements to the contrary, the increasing incidence of hiatus hernia has not been accompanied, to the present writing, by any comparative increase in the number of carcinomas of the stomach associated with hiatus hernia. A recent review of the literature reported only 46 cases.[1] However, the location of the lesion was mentioned in 32 cases and, of these, 28 were in the cardia of the stomach. This is a striking increase in the usual proportion of 10% of carcinomas of the stomach arising in the cardia. Therefore, although the incidence of gastric carcinoma is not greater, the involvement of the cardia in the majority of these cases may be significant. In England attention has been directed to the infrequency of the association of hiatus hernia and carcinoma;[2,3] until 1951 only 10 cases were reported. Allison, whose work on esophageal hiatus hernia is well known, refers to carcinoma in the herniated stomach as "rather rare."[4] A more recent report in a British journal emphasized the association of carcinoma of the cardia with hiatus hernia. Reviewing the literature, Smithers[5] reported that in the group with sliding hernias, 28 carcinomas were located at the cardia and only nine were found in the rest of the stomach. (Two of these were leiomyosarcomas.) In those cases where the type of hernia was not specified, there were 13 lesions at the cardia and 14 located in the rest of the stomach, also indicating a marked increase in the frequency of lesions of the cardia. By contrast, para-esophageal

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hernia, much less common than the sliding variety and developing with a true hernia sac, was associated with three cases of gastric tumors, none located in the cardia.

There are three possible explanations for the association of carcinoma of the cardia and hiatus hernia: first, that the relationship is coincidental; second, that hiatus hernia may in some way predispose to the development of carcinoma; and third, that the carcinoma precedes the hiatus hernia and its continued growth produces a lax hiatus, reflex contraction of the esophagus and herniation.

This report describes two cases in which this association of carcinoma of the cardia of the stomach and hiatus hernia was found. In the first patient there is evidence, in view of the traumatic history, that the hiatus hernia, although asymptomatic, probably did precede the carcinoma.

The association of the two conditions is reported, first, to discuss their possible relationship, and second, to point out that the importance of this association should not be exaggerated. The complications of hiatus hernia have been frequently described and obviously are not to be taken lightly, but the possibility that carcinoma may be a complication is not, for the present time at least, a relationship that should be emphasized.

Case Reports

Case 1. A 46 year old white male truck driver was referred with a history of dysphagia of two months' and vomiting of one month's duration. The onset was abrupt, with an increasing dysphagia for solids and later for liquids. Vomiting developed gradually and was related to the ingestion of solid food. There was never any history of blood in the vomitus or of tarry stools. There had never been any complaint of abdominal pain. Occasionally, however, for the last several months he had complained of heartburn. During the period of his present illness he lost 25 pounds, his present weight being 211 pounds. Past history included the fact that at the age of 11 he had been run over by a horse-drawn buggy. An abdominal operation was performed but the nature of the findings could not be ascertained.

Physical examination revealed a well nourished, obese male in no apparent discomfort. Blood pressure was 134/80 mm. of Hg. The abdomen revealed a broad left upper rectus scar; no masses were palpable, and there was no rigidity or tenderness throughout. Rectal and sigmoidoscopic examinations were negative. Laboratory investigation revealed a hemoglobin of 15 gm. and a white blood cell count of 10,400, with a 70% polymorphonuclear count. A stool was negative for occult blood. Gastric analysis disclosed 50 units free hydrochloric acid and a 2 plus benzidine (Gregerson). Barium meal examination revealed a shortened esophagus that narrowed abruptly 8 cm. above the left diaphragmatic leaf. The esophageal pouch proximal to the constriction was dilated, and presented a pressure defect on the right inferior surface. The contour of the left margin was more rounded but with a sharp projection. The constricted segment was 2 cm. in length and the mucosal pattern was destroyed; the lumen was not distensible. Distal to this narrowed area was a hiatus hernia measuring 6 cm. in diameter, not reducible in the erect position. No ulceration in the hernia could be visualized. The remainder of the stomach presented no obvious abnormality. The impression was carcinoma of the cardia of the stomach in association with an esophageal hiatus hernia (figures 1 and 2). Esophagoscopy was performed and revealed an ulcerating lesion at 32 cm., suggesting carcinoma. The esophageal mucosa appeared normal. Biopsy of the lesion disclosed mucus cell adenocarcinoma of the stomach. Exploration was performed through a thoracotomy incision. A large carcinomatous mass was found, located at the cardia of the stom-

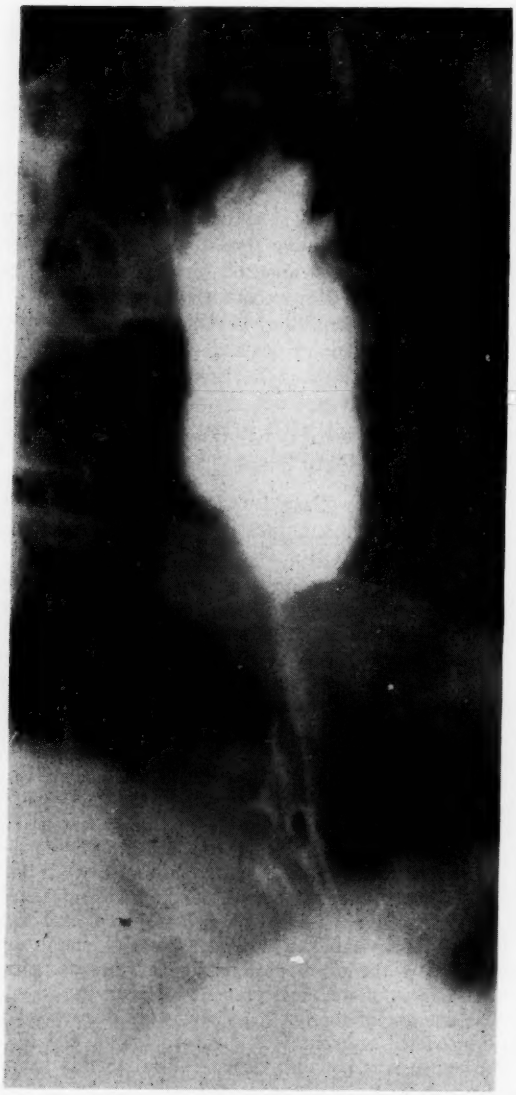

FIG. 1. There are marked narrowing and rigidity at the distal esophagus. Pressure defects are visualized on both inferior margins of the esophageal pouch. The mucosal pattern is destroyed in the constricted segment. Impression was carcinoma of the cardia.

ach and extending along the esophagus into the posterior mediastinum. The mass extended into the right as well as into the left pleural cavity. Large, hard lymph nodes were present on the thoracic aorta and over the left gastric artery. The lesion was considered inoperable.

Case 2. A 51 year old white male office worker presented himself with a three months' history of dyspepsia, abdominal pain and dysphagia. The onset of pain was gradual, localized to the upper abdomen and burning in character, usually occurring one hour following meals. The pain became only slightly worse, but after two months was associated with dysphagia for solid foods. On several occasions the obstruction was relieved by vomiting. The patient had suffered a weight loss of 12 pounds during the present illness. Physical examination revealed some localized upper abdominal resistance but was otherwise negative. Laboratory examination was essentially normal. Barium meal examination revealed a narrowing at the terminal esophagus approximately 6 cm. above the diaphragm. There was no proximal dilatation, and the esophagus was not displaced. The constricted area measured 6 mm. in diameter and was rigid, and extended for approximately 1.5 cm. in length. The mucosa in this area could not be visualized adequately. Immediately below the constriction a hiatus hernia measuring 4 cm. was visualized. There were no obvious ulcerations or diverticula within the herniated pouch. The remainder of the stomach was normal. The duodenal cap filled completely and presented no abnormality. The impression was hiatus hernia with esophagitis, but the possibility of carcinoma could not be excluded. Esophagoscopy was not performed.

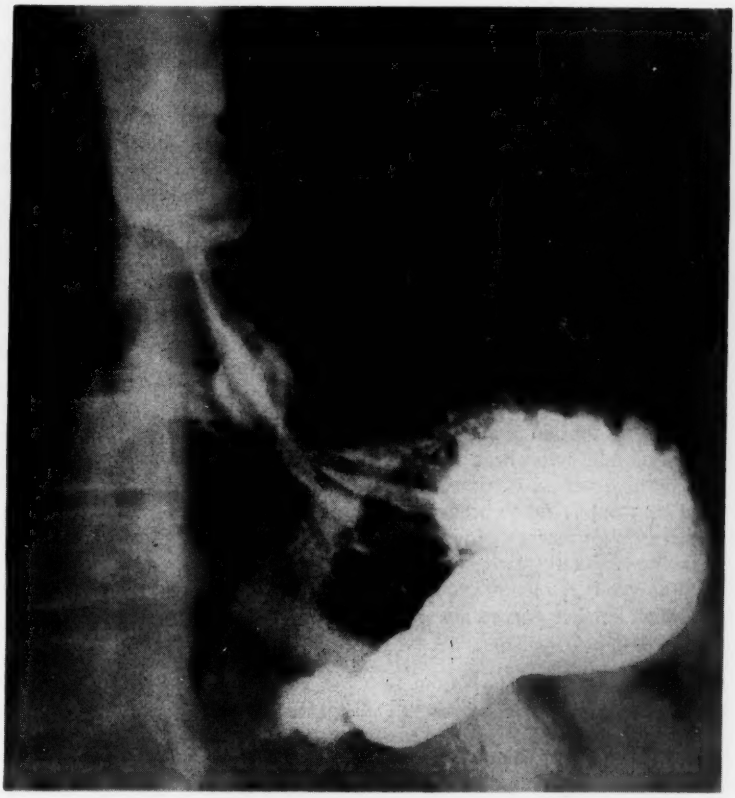

FIG. 2. The esophagus is dilated proximal to the constriction at the esophagogastric junction. The hiatus hernia is well visualized.

Medical therapy was of no benefit, and the patient was operated on for the repair of an hiatus hernia. A mass the size of a walnut was encountered at the cardia of the stomach. The tumor was resectable and an esophagogastrectomy was performed. The pathologic diagnosis was adenocarcinoma. At the present time, six months following surgery, the patient is alive and apparently well.

Discussion

That the carcinoma at the gastric cardia precedes the hiatus hernia and by its growth produces a lax hiatus, followed by reflex contraction of the esophagus with development of the hernia, appears to be the explanation of choice. This would seem to follow from the clinical data that reveal a much higher incidence of gastric carcinoma at the cardia in association with hiatus hernia than is generally the rule in carcinoma without hiatus hernia. Barrett [6] has already emphasized that the abdominal pressure from below with the negative pressure (suction) from above predisposes to the formation of hiatus hernia. Even though there may not be a lax hiatus to begin with, an abdominal tumor presenting at the esophageal opening may be a decisive influence in producing the hernia. The only argument against such a development might be the factor of infiltration and fixation around the tumor. However, by exercising traction on the adjacent structures this may be a positive element in the development of the hiatus hernia, rather than a negative influence. At the same time, the fact that carcinoma of the cardia often spreads up into the esophagus may also exaggerate the tendency to produce herniation. Nevertheless, hiatus hernia may precede the development of carcinoma in the stomach, apparently as a fortuitous association. In the first case, although one cannot unequivocally state that a hiatus hernia preëxisted, the history of abdominal trauma makes it more likely that hiatus hernia was present in this patient prior to the development of the malignancy. Another patient with carcinoma at the cardia and hiatus hernia has been observed in whom roentgen examination several years previously revealed only a hiatus hernia.

It is interesting that in none of the cases previously reported is there mention of the finding of esophagitis, and in neither of the cases reported in this paper was there any evidence of esophagitis. While the latter occurs infrequently, it would appear that in a series of approximately 50 patients several cases of esophagitis should have been present if the hiatus hernia had preëxisted for any considerable period of time. On the other hand, the presence of a tumor at the cardia would tend to prevent reflux of gastric contents, the usual cause of esophagitis in the presence of hiatus hernia. These facts suggest that the hiatus hernia in the majority of these instances is a sequel to the development of the tumor, although it does not exclude the reverse, which undoubtedly does occur but in a much smaller percentage of cases.

Summary

1. Two cases of carcinoma of the cardia of the stomach in association with hiatus hernia are presented.

2. Despite the increasing incidence of esophageal hiatus hernia (sliding) following barium meal examination, there does not appear to be a comparative increase in the number of patients with carcinoma of the stomach.

3. It is presumed that in the vast majority of cases when the two conditions are associated, carcinoma of the cardia precedes and is followed by the development of a hiatus hernia.

SUMMARIO IN INTERLINGUA

Es reportate le casos de duo patientes in qui esseva constatate le association de carcinoma del cardia del stomacho con hernia del hiatus esophagee. In un del casos, le historia del patiente suggereva pre-existentia de hernia hiatal a causa traumatic, sed le diagnose preoperatori, confirmate durante le intervention chirurgic, esseva carcinoma in association con hernia hiatal. In le altere caso, un constriction visualisate in le examine roentgenologic suggereva esophagitis, sed carcinoma esseva trovate al tabula de operationes.

Ben que meliorate technicas radiologic ha resultate in un marcate augmento del diagnoses de hernia per le hiato esophagee, le incidentia de carcinoma del stomacho in association con iste anormalitate ha non experientiate un augmento proportional. Un revista del litteratura ha resultate in le discoperta de solmente 48 reportos de tal casos. Le location del lesion esseva mentionate in 32 casos. Inter istos, 28 (i.e. plus que 85%) esseva in le cardia del stomacho. Isto contrasta con le facto que le cardia es afficite in solmente 10 a 15% de omne casos de carcinoma del stomacho. In plus, nulle del reportos de carcinoma del cardia in association con hernia per le hiatus describe esophagitis como constatation operatori, ben que esophagitis es un complication in un alte procentage del patientes con hernia a glissage per le hiatus. Le datos clinic supporta le conclusion que carcinoma del cardia occurre como phenomeno primari que resulta, per su crescentia, in un laxe hiato, in un contraction reflexe del esophago, e assi secundarimente in le formation del hernia hiatal. Il is importantissime signalar que hernia hiatal non pare predisponer al disveloppamento de carcinoma del stomacho.

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CHOLESTEROL PERICARDITIS *

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CHOLESTEROL pericarditis is a very rare disease and, at present, very poorly understood. Reports of only 11 cases have appeared in the world literature,

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four of them in American medical journals.[1, 2, 3, 9] The first reported autopsy was done on one of the latter cases. The present case is the twelfth reported, and the second in this country in which an autopsy was performed. It is therefore understandable that the disease at this time is far from being well known, especially from the standpoint of pathogenesis. This will be discussed in more detail later in this paper.

Case Report

The patient was first seen on May 2, 1947, at the age of 60, complaining of inconstant pain in the right lower quadrant of 20 years' duration. Past history included mumps, measles, smallpox, "flu," typhoid fever and malaria. Physical examination at that time revealed the patient's weight to be 156½ pounds; blood pressure, 130/80 mm. of Hg. General physical examination revealed no abnormality except relaxed inguinal rings. A fluoroscopic examination of the chest showed a few calcified areas in both upper lobes; the heart was normal in size. Laboratory examinations included a white blood count of 6,600 per cubic millimeter, and differential count of 5 stabs, 62 segmented forms, 17 lymphocytes, 6 monocytes and 10 eosinophils. Repeat differ-

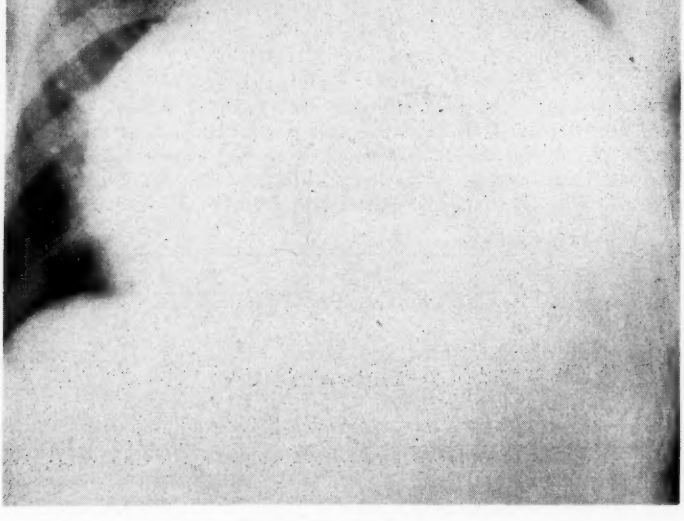

Fig. 1. X-ray of chest.

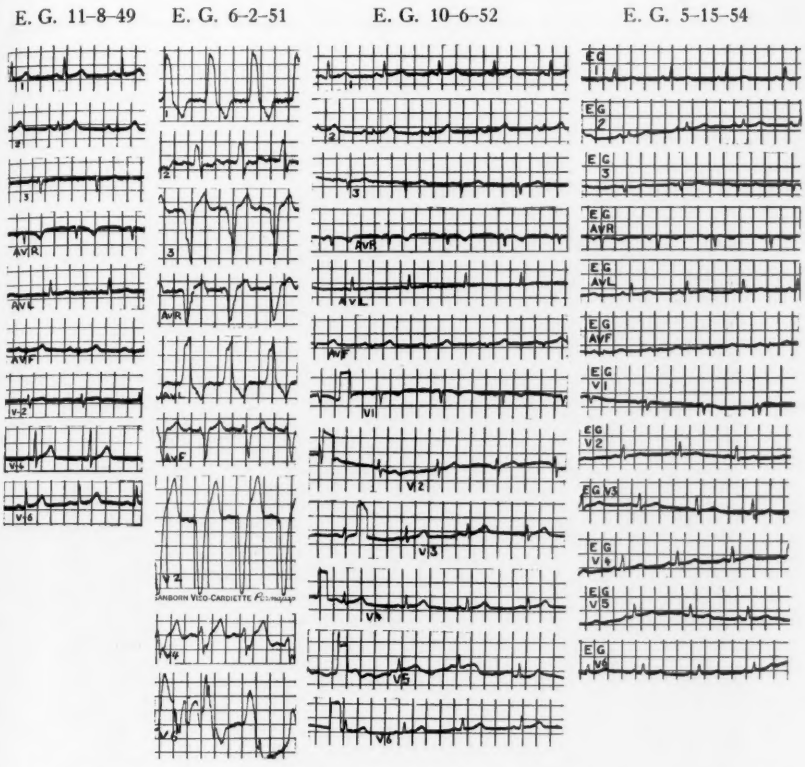

FIG. 2. Electrocardiograms showing transient left bundle branch block on June 2, 1951.

ential count revealed 4 stabs, 47 segmented forms, 30 lymphocytes, 7 monocytes and 12 eosinophils. Barium enema showed a congenital anomaly of the colon, with a long, mobile sigmoid and a long, redundant transverse colon. The patient was then referred to a urologist for further evaluation regarding the pain. His examination revealed prostatitis, which was treated. The patient improved and had no further genitourinary symptoms. Heart, lungs and abdomen remained normal on subsequent examination, and he did not feel ill until March 16, 1949, when he complained of headaches, cough and some chest pain, not aggravated by deep breathing. Examination revealed heart and lungs to be normal.

The patient was seen again on July 19, 1949, at which time he complained of several weeks' illness consisting of weakness and "crowding in the chest." Blood pressure was 110/66 mm. of Hg. Cardiac dullness was found to extend to the left anterior axillary line. Heart tones were soft. No friction rub was heard. Fluoroscopic examination and chest roentgenogram revealed a globular cardiac silhouette occupying about three fourths of the chest width (figure 1). There was very little movement at the periphery of the pericardial sac. The patient was sent to Christian Welfare Hospital for a period from July 20, 1949, to August 23, 1949, at which time two pericardial aspirations were done. About 100 c.c. of a straw-colored fluid were

obtained and were sterile on culture. Nothing unusual was noted about the fluid at that time. The patient refused to submit to further aspirations.

During this stay in the hospital the spleen was easily palpable, but on September 17, 1949, was not large enough to palpate. Fluoroscopic examination revealed the cardiac silhouette to be as large as seen previously. The patient returned to work in November, 1949, and experienced little difficulty except for some weakness. Re-examination every two months failed to show any change in heart size. On February 13, 1951, he complained of dizziness upon light exertion. There was a trace of periph-

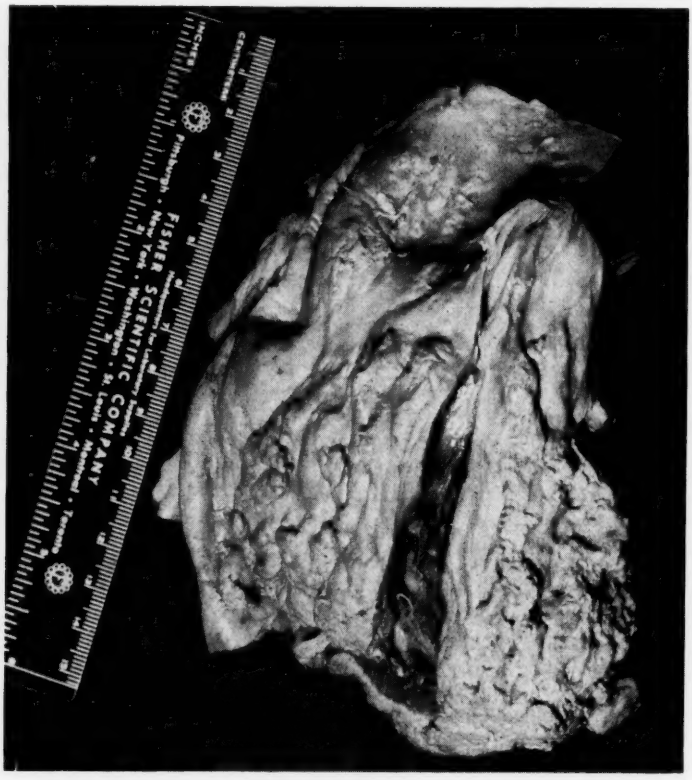

FIG. 3. Opened pericardial sac showing shaggy cholesterol deposits.

eral edema at this time. Mercuhydrin was administered twice weekly intramuscularly, and later once a week, with a moderate clinical improvement. Electrocardiograms had been normal except for moderately low voltage. On June 2, 1951, an electrocardiogram showed left bundle branch block. Subsequent electrocardiograms showed a return to normal except for persistent low voltage (figure 2).

The patient continued to work steadily and felt very well until March, 1954, at which time he noticed pain across the chest on inspiration. Mercurial diuretics, which had not been used for two years, were started again. A chill occurred following the third injection. Subsequent administration of all mercurial diuretics, including

oral types, produced very severe reactions, characterized by chills, extreme restlessness, and a burning sensation of the skin. Mercurial diuretics were discontinued. An attempt at digitalization was unsuccessful because of severe nausea, resulting from only a few doses. The patient was admitted to St. Mary's Hospital on June 4, 1954, because of marked increase in dyspnea, ankle edema and anorexia. He improved very little and was discharged on July 16, 1954. He was followed at home

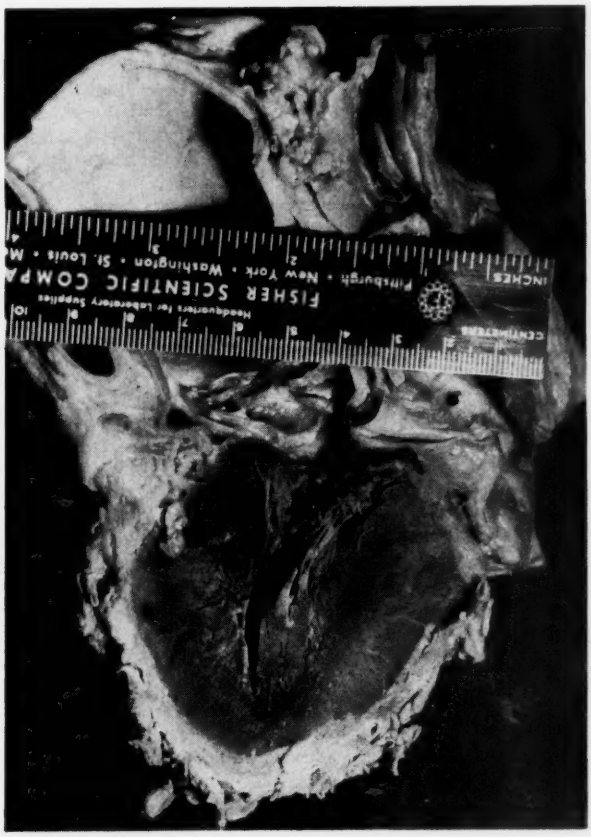

FIG. 4. Cross-section of left ventricular myocardium.

and remained refractory to all types of treatment aimed at producing diuresis and relieving dyspnea. Oxygen gave moderate relief. A state of continued, severe restlessness was aggravated by all sedatives. Demerol gave limited relief. Massive peripheral edema remained and became more severe, involving the hands and lower arms in October, 1954. He was admitted to St. Mary's Hospital again on October 29, 1954, in a stuporous state. Respiratory rate was increased to 32 per minute, and moist râles were heard over both lung fields. The patient became steadily worse and died on November 14, 1954.

Autopsy Findings:

External Examination: The body was that of a well developed, well nourished white male. The head showed nothing remarkable and the hair was abundant. The upper extremities were symmetric. The lower extremities revealed a marked edema which extended up to about the midthighs. The thorax was not remarkable. The abdomen was slightly protuberant. The external genitalia appeared normal for the age of the patient.

Internal Examination: When the body was opened the most striking thing was a very large pericardial sac which contained 1,500 c.c. of turbid yellowish fluid. The sac measured 28 cm. in width and 23 cm. from the upper limits to the diaphragmatic level. The parietal wall of the pericardium was thickened and fibrous. The inner surface contained many yellowish brown soft patches resembling cholesterol deposits. The heart was not grossly enlarged and weighed 260 gm. The visceral pericardial surface was coated by a thick, yellowish, shaggy papillomatous material which varied from 0.5 cm. to 1.3 cm. in thickness (figure 3). Sections revealed no dilation of the cardiac compartments. The myocardium was of fairly good tone. The valves were not remarkable except for thickening of the anterior cusp of the mitral valve due to slight deposit of cholesterol. The endocardium was not thickened. The myocardium of the left ventricle was thickened and measured up to 20 mm. in thickness (figure 4). The ascending aorta contained a few atheromatous plaques, and the descending portion contained frequent atheromatous plaques, but no calcification could be demonstrated. Serial sections of the coronary arteries revealed patchy atheromata, but the lumen appeared patent throughout. Each pleural space contained approximately 500 c.c. of thin, straw-colored fluid. The lungs showed a marked compression atelectasis; on section they were slightly nodular. The cut surface of both lungs revealed small areas of firm tissue which were interpreted as bronchopneumonia. The peritoneal cavity contained 1,200 c.c. of straw-colored fluid. The peritoneal surface revealed no yellowish plaques and was fairly smooth and glistening. The spleen weighed 375 gm. Its capsule was smooth, and the cut surface revealed a moderate degree of congestion. The liver weighed 2,000 gm. and was grossly enlarged. The surface was smooth. On section the cut surface revealed a typical nutmeg appearance characteristic of a long-standing passive congestion. The biliary system was essentially normal. The pancreas was not remarkable. The gastrointestinal system was essentially negative except for postmortem autolysis of the gastric mucosa. The adrenals were normal in size and shape. On section they revealed no evidence of adenoma or other pathologic process. Both kidneys were in their normal positions and both were normal in size and shape. On section their capsules were easily stripped, revealing a fairly smooth surface. The cut surface showed normal, distinct markings. The pelvis of each kidney and the ureters were essentially normal. The urinary bladder contained 300 c.c. of clear urine. The mucosa was essentially normal. The prostate was slightly enlarged and nodular; on section, however, it was soft and loculated. The internal genitalia were not remarkable. There were no enlarged lymph nodes in the retroperitoneal spaces. Dissection of the neck revealed a normal thyroid gland. No adenomata or other pathology could be demonstrated.

Microscopic Examination: Microscopic examination of the parietal pericardium revealed numerous cholesterol clefts overlying an area of histiocytes containing foamy cytoplasm. Occasional lymphocytes were present, and the connective tissue was moderately edematous. The visceral pericardium revealed areas of hyaline degeneration and areas containing huge deposits of cholesterol clefts. Some of these areas consisted of pure cholesterol deposits, while others were surrounded by histiocytes (figure 5). There was infiltration with lymphocytes, and an occasional foreign body giant cell was present. Plasma cells were not infrequent but polymorphonuclear leukocyte were not seen. The pericardial fat beneath the deposit of cholesterol in

some areas appeared fairly normal, while in others there was a low grade chronic inflammatory reaction consisting mostly of lymphocytic and plasmacytic infiltration. The myocardial fibers were hypertrophied. Frozen sections of the visceral pericardium stained with scarlet red gave a positive test for lipid. Iron stains revealed the presence of small scattered deposits of iron. The sections of the lungs revealed a moderate degree of atelectasis, patchy areas of edema and bronchopneumonia. Numerous sections throughout different areas of the lung failed to show any evidence of tuberculosis or other infectious granulomata. In the liver there was a marked degree

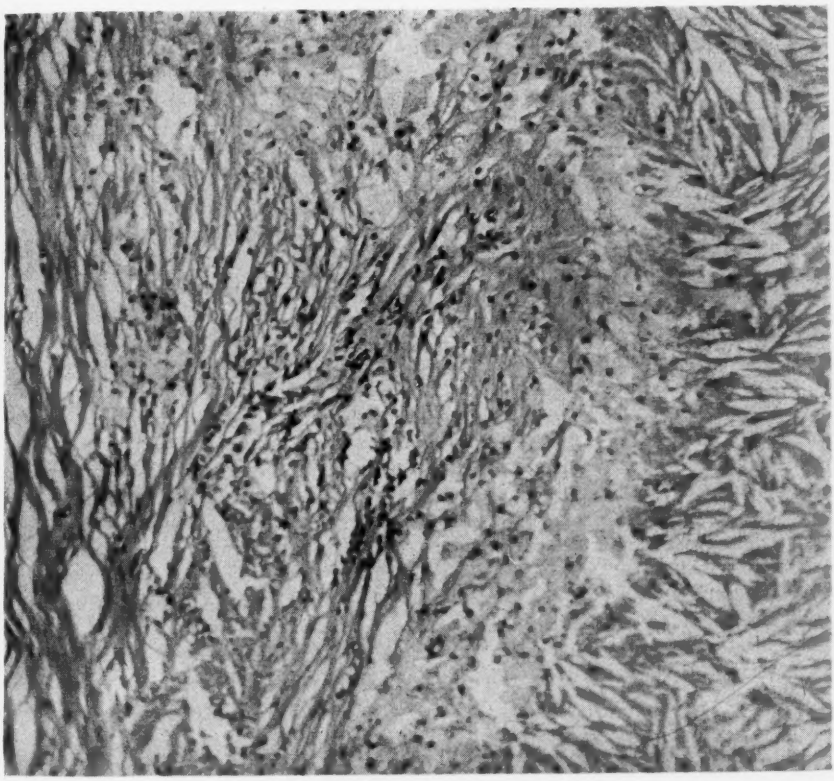

FIG. 5. Microscopic appearance of parietal pericardium showing cholesterol clefts.

of chronic passive congestion. The spleen showed congestion. The kidneys revealed a moderate degree of arteriolonephrosclerosis. The prostate revealed benign hyperplasia with no evidence of malignancy. Sections of the other organs revealed nothing striking and were consistent with the gross anatomic findings. Cultures made of the pericardial fluid and pleural fluid were sterile.

Anatomic Diagnoses: Cholesterol pericarditis; arteriosclerosis; left ventricular hypertrophy; hydrothorax and hydroperitoneum; bronchopneumonia; atelectasis; edema of the lungs; chronic passive congestion of the spleen and liver; benign arteriolosclerosis of the kidneys; benign hyperplasia of the prostate gland.

Discussion

Considering the relatively good condition of the heart in this case, the patient may well have survived if further aspirations could have been done. Ada [1] reports a case of massive pericardial effusion on whom a thoracotomy was done, followed by complete recovery. A biopsy of the pericardium showed cholesterol plaques on the visceral and parietal surface, and the fluid was sterile. This case revealed no myxedematous features, and the basal metabolism rate was plus 7%. Merrill [2] reported a case of pericardial effusion on whom aspirations were done, revealing "innumerable cholesterin crystals." This patient's appearance was said to be myxedematous. Howard [3] in 1946 reported the first case of cholesterol pericarditis in this country in which an autopsy was performed. He stated that this was a case of myxedema and that the pericardial fluid contained cholesterol crystals, while "both pericardium and epicardium were covered with soft orange-yellow, conelike deposits of cholesterol."

Others [4, 5] have reported cases of myxedema associated with pericardial effusion in whom administration of thyroid extract brought about clinical recovery and disappearance of the fluid from the pericardial sac. Feasby's [6] case in 1940 revealed a small pericardial effusion, but with a heart enlarged as a result of myxedema. Gordon [7] in 1929 described a case of pericardial effusion accompanying myxedema. Fluid aspirated from the pericardial sac in Feasby's and Gordon's cases failed to reveal cholesterol crystals. Our case showed no features of myxedema; in fact, his temperament and physical findings suggested a euthyroid or slightly hyperthyroid state.

From the foregoing it is easy to see that, although myxedema, pericardial effusion and cholesterol pericarditis are often associated, it cannot be stated at present that myxedema is the etiology of cholesterol pericarditis in all cases. The evidence for an infectious etiology is completely lacking. Furthermore, there is no explanation for failure of the electrocardiogram to show features consistent with pericarditis in some cases and not in others, unless those that showed ST segment and T-wave changes may have resulted from associated myxedema heart disease. An interesting contribution was made by Ehrenhaft and Taber,[8] who injected a crystalline suspension of cholesterol into the pericardial sacs of two dogs, which later showed pericardial effusion, pericardial granulation tissue and pericardial and epicardial thickening. Creech and his associates [9] in a recent paper report the successful treatment of cholesterol pericarditis by pericardiectomy.

Conclusion

A case of cholesterol pericarditis is presented, with clinical course and autopsy findings. Etiology and pathogenesis are both obscure, although myxedema is often found to be associated with cholesterol pericarditis. It would appear that further extension of our knowledge of this disease might result in the survival of almost all cases, by means of surgery, by removal of pericardial fluid by aspiration, or by the administration of thyroid.

Summario in Interlingua

Pericarditis a cholesterol es un morbo rarissime e pauco comprendite. Le presente caso es le dece-secunde unquam reportate. Illo es le secunde autopsiate in le Statos Unite.

Le patiente esseva primo vidite le 2 de maio 1947, sin symptoma referibile a ille tempore al thorace e sin anormalitates constatabile per le examine physic, excepte prostatitis. Le 17 de martio 1949, ille se plangeva de tusse e dolores thoracic. Le corde e le pulmones esseva examinate e se monstrava normal. Le 19 de julio 1949, ille se plangeva de "repletion intra le thorace" e de debilitate. Le roentgenogramma thoracic revelava un silhouette globular del corde que occupava tres quartos del amplor del thorace. Aspiration del sacco pericardial produceva 100 cm^3 de un liquido de color jalne de palea que se monstrava sterile in culturation. Le patiente refusava aspirationes additional.

Subsequentemente ille esseva vidite plure vices. Le electrocardiogrammas, excepte sub basse voltages, esseva normal usque al 2 de junio 1951 quando signos electrocardiographic de bloco del branca sinistre esseva notate. Plus tarde le electrocardiogrammas esseva de novo normal.

In martio 1954, le patiente habeva dolores thoracic, dyspnea, e edema de cavilia. A iste tempore, omne diureticos mercurial produceva algor, disquietude, e arditura del pelle. Quando digitalis esseva tentate, illo produceva sever grados de nausea. Solmente le administration de oxygeno effectuava un moderate alleviamento. Le patiente sequeva un curso de deterioration progressive e moriva le 14 de novembre 1954.

Al necropsia un largissime sacco pericardial esseva constatate que contineva 1.500 cm^3 de un turbide fluide jalnastre. Le superficie interior del pariete contineva jalnastro-brun depositos de cholesterol de un spissitate de 0,5 a 1,3 cm. Le corde non esseva allargate. Le arterias coronari esseva patente. Le pulmones exhibiva atalectasis compressional. Parve areas de bronchopneumonia esseva presente. Le superficie esseva lisie. Le splen e etiam le hepate se monstrava congestionate. Le hepate esseva allargate a 2.000 g. Le glandulas adrenal, le renes, e le vesica urinari esseva normal. Le prostata monstrava loculation. Le glandula thyroide esseva normal. Le pericardio visceral exhibiva enorme depositos de crystallos de cholesterol in fissuras. Culturas del fluido pericardial e pleural esseva sterile.

Il es possible que iste patiente haberea supervivite si aspirationes additional habeva essite autorisate. Ada, Merrill, e Creech ha reportate casos con successo de tractamento per thoracotomia, aspirationes, e pericardiectomia, respectivemente. In iste e altere casos, certe patientes habeva myxedema, alteres non lo habeva.

Pericarditis a cholesterol es obscur in etiologia e pathogenese, ben que myxedema se trova frequentemente in association con illo. Intervention chirurgic, aspirationes, o administration de extracto thyroide (si usate correctemente) va forsan provar se capace a salvar quasi omne le patientes con iste morbo.

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TOXIC HEPATITIS AND AGRANULOCYTOSIS DUE TO CINCHOPHEN *

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CINCHOPHEN (phenylcinchoninic acid) was first synthesized by Doebner and Giesecke in 1887 and was introduced into the therapeutic armamentarium by Weintraub in 1911 as a uricosuric agent in the treatment of gout, and has been prescribed for rheumatoid arthritis, rheumatic fever, headache, neuritis, etc. In the two or three decades after its introduction cinchophen was used extensively in both prescribed and patent medications, despite the fact that attention had been called as early as 1923 to its serious undesirable side-effects. In that year Worster-Drought [21] reported a case of toxic hepatitis due to cinchophen administration. Up to 1948 approximately 230 such cases, with an associated mortality rate of almost 50%, had been reported.

Much less common are the reported cases of cinchophen-induced agranulocytosis. Five such instances were found in a search of the literature.[2, 5, 11, 14, 16] Only the first of these resulted in a fatality. The agranulocytosis in this case was reportedly due to an intravenous injection of ortho-iodoxybenzoate, which contains phenylcinchoninic acid. Although Coventry [2] reported his case as one of "granulocytopenia" due to cinchophen ingestion, he mentioned that his patient had slightly icteric sclerae and an icterus index of 14. Another salient feature of his report was that the patient, a 63 year old white male, had a strong history of alcoholism. This possibly accounted for the jaundice. The liver in this case was not palpable.

The patient reported herein represents the first case of combined liver and bone marrow damage due to cinchophen sensitivity reported as such, although Coventry mentioned the possibility of this occurrence in his 1939 article.

CASE REPORT

A 59 year old white unmarried female schoolteacher had been well constitutionally until about three weeks prior to her admission to the Hospital of the University of Pennsylvania on July 6, 1955. On June 16 she developed and recovered from a short bout of fever. Ten days later the fever returned, this time accompanied by anorexia and malaise, which were present on admission. Her family physician gave her some oxytetracycline for this condition about one week before admission. Also at that time the patient noted that her urine had become darker and her stools lighter. One day prior to hospitalization she was seen again by her doctor, was observed to be markedly icteric, and was referred to this hospital for treatment.

The patient knew of no recent previous contact with a jaundiced person. Six weeks and five weeks, respectively, before admission she had been given an intra-articular injection of hydrocortisone into her arthritic knees. She had had no other parenteral injections in recent months. She denied contact with cleaning fluids or

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similar substances. There was no history of gall-bladder disease. She had never been jaundiced before.

Having suffered with rheumatoid arthritis for the last 15 years, the patient had been treated by innumerable physicians. She had taken acetylsalicylic acid at various times and obtained some pain relief therefrom. Some time ago, after two weeks of oral cortisone, she had developed pain in the right upper abdominal quadrant, and this drug had been discontinued. There had never been any melena or hematemesis. She had never taken phenylbutazone to her knowledge. In April, 1949, according to her family physician, she had taken a prescription containing cinchophen, without any apparent ill effects. On June 17, 1955, the patient had started taking the following prescription every four hours and continued this for approximately 10 days:

Phenylcinchoninic acid	gr. 7½
Potassium iodide	gr. ½
Phenobarbital	gr. ¼
Niacinamide	gr. ½

Systemic review was otherwise noncontributory. Past medical history, family history and social history were negative. The patient used alcoholic beverages very infrequently.

On initial physical examination the patient was found to have a temperature of 99.6° F., a pulse rate of 100/min., a respiratory rate of 22/min., and a blood pressure of 150/80 mm. Hg. She was five feet tall and weighed 148 pounds. She was perfectly oriented and clear mentally. The skin, mucous membranes and sclerae were markedly icteric. The liver edge was felt 5 to 6 cm. below the right costal margin, and was smooth, fairly firm, and tender to palpation and percussion. The spleen was just palpable below the left costal margin, but was not tender. Evidence of old arthritic changes was seen in the slight deformities of the fingers of both hands and in the limitation of flexion and extension in both knees. Inflammation or ulceration of the oral and nasal mucosa or of the perianal region was notably absent. There was some telangiectasia of the cheeks, but nowhere else was this noted.

Initial Laboratory Studies: Hematologic procedures revealed a hemoglobin of 10.9 gm., a red blood cell count of 4,000,000, a platelet count of 338,000, and a white blood cell count of 800, with 76% lymphocytes, 16% neutrophils, 4% eosinophils and 4% monocytes. The differential count was based on a tabulation of only 25 leukocytes. A repeat white count on the following day showed 1,000 cells. Liver survey at the time of admission and shortly thereafter demonstrated the presence of hepatocellular damage and intracanalicular obstructive changes (figure 1 and table 1). The blood urea nitrogen and serum electrolytes were normal; serologic tests for syphilis were negative.

Because of the marked leukopenia and neutropenia, a sternal marrow examination was performed on the second hospital day. This study showed a marked decrease in the number of the cells of the granulocytic series except for the eosinophils and their precursors (figure 4). Erythroid elements and megakaryocytes were present in normal numbers. There was a relative abundance of lipoid histiocytes.

Hospital Course: On the second day after admission the patient's jaundice deepened somewhat and she developed pruritus. She became severely nauseated for the first time in her illness, and was anorexic to the point of refusing her lunch. In view of the apparent gravity of the liver damage, it was decided to start 10% glucose in water intravenously and cortisone orally.

There was a fairly rapid recovery of the bone marrow, so that the white blood cell and differential counts were within normal limits on the tenth hospital day (figure 2). The white count continued to rise and eventually reached a peak of 19,400 about

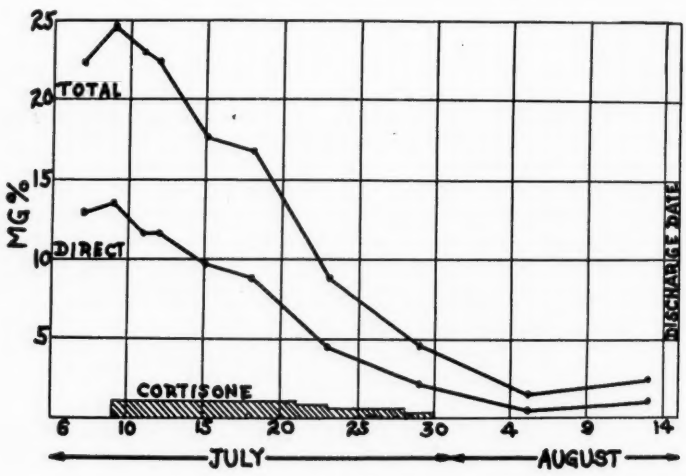

FIG. 1. Serum bilirubin levels in mg. %.

two weeks after entry. At the time of discharge the white count was 9,200 and the differential was still normal.

On the sixteenth hospital day the patient developed a generalized, patchy-to-diffuse, erythematous, macular, pruritic rash, which became more confluent within 24 hours and then faded completely within one week.

The jaundice gradually cleared and the liver status showed progressive improvement over the ensuing weeks (figure 1 and table 1) so that the total serum bilirubin at the time of discharge on the forty-first hospital day was 2.3 mg. %. Although the liver was palpable even at the time of discharge, it had started to diminish in size a few days after admission and continued to get smaller slowly over the weeks. Clinically, the patient became symptom-free after one week and exhibited steady improvement for the remainder of her hospitalization except for the rash described above. She was discharged to a convalescent home after six weeks of hospitalization.

Additional studies done during this hospitalization included three urinalyses, which were essentially negative except for the presence of bilirubin in all three and a trace of albumin in one specimen. A chest x-ray showed no evidence of active disease. An electrocardiogram was normal. X-ray of both knees on August 10 re-

TABLE 1

Other Liver Status Studies	Normal Range	Units	7/7	7/9	7/11	7/23	7/29	8/11
Cephalin floc.	0 to +/−	amt. floc.	++++	—	—	—	—	+/−
Thymol floc.	0 to +/−	amt. floc.	+	—	—	—	—	0
Thymol turb.	0 to 5.5	Sh.-Hoag.	12.8	—	—	—	—	12.6
Zinc turb.	0 to 9.6	Sh.-Hoag.	12.2	—	—	—	—	9.6
Alk. phos.	2.2 to 8.5	Shinowara	13.3	—	—	—	8.5	—
Cholesterol	117 to 333	mg.%	—	139	139	—	—	—
Cholest. esters	60 to 75%	mg.%	—	—	107	—	—	—
Prothromb. time	14 to 15 sec.	% normal	—	80+/−13	100+/−13	—	—	—
Proteins, total	6.3 to 8.3	gm.%	—	6.9	—	—	—	—
Alb./glob.	3.5–4.7/2.1–4.1	gm.%	—	3.3/3.6	—	—	—	—
Fast. bl. sugar	65 to 105	mg.%	48	—	159*	75	—	—

* High intake of oral and intravenous glucose.

vealed mixed arthritic changes, with considerable subchondral bone resorption in the medial aspect of each knee. The picture was a combination of rheumatoid disease with degenerative change.

Treatment: The patient was kept in bed for four weeks. Large doses of all the vitamins were administered. Crude liver extract (intramuscular) was also given daily for more than two weeks. Vitamin K (10 mg. intramuscularly, twice a day) was given for 12 days. Prophylactically, penicillin (600,000 units intramuscularly, twice a day) and tetracycline (250 mg. orally, four times a day) were administered for 10 and nine days, respectively. Cortisone was started on the third hospital day,

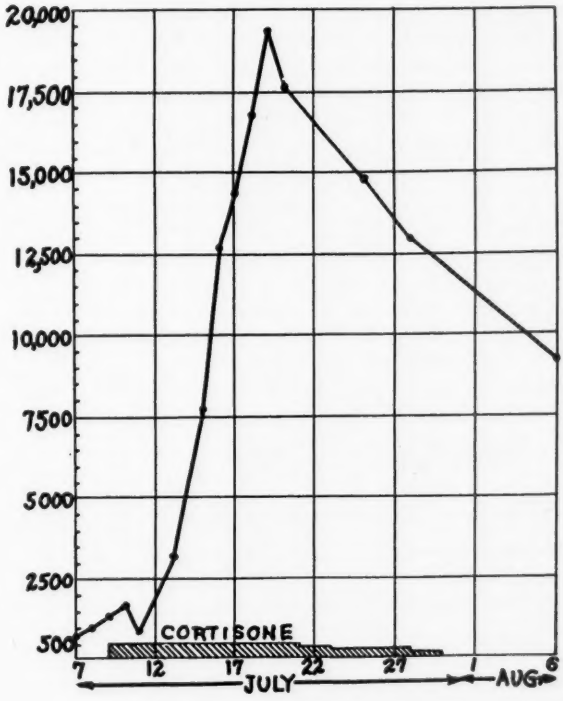

FIG. 2. White blood cell count.

was continued at 25 mg. orally four times a day for about two weeks, was gradually tapered off for one week, and was then stopped altogether. Antihistaminics were given for symptomatic relief.

DISCUSSION

The toxicity of cinchophen has been considered to be the result of idiosyncrasy or hypersensitivity to the drug.[6] The patient reported here had taken cinchophen five years previously, without untoward reaction. Thus, sensitivity to the drug may not be manifest after the first ingestion of the drug, but may appear after subsequent intake. This phenomenon has been reported frequently in the literature.[6, 11]

Although the mechanisms of the toxicity of this drug have not yet been satisfactorily elucidated, the majority of authors contend that it is perhaps the in vivo liberation of free benzene or nitrophenols that is responsible for the toxic degeneration of liver tissue and the leukopoietic suppression. Kracke[9] and various other investigators have shown experimentally that these substances do have such effects. The chemical structure of cinchophen gives plausibility to this theory.

The effect of the therapeutic regimen upon the patient's liver status is difficult to evaluate accurately. Bed-rest and a very high carbohydrate intake possibly enhanced the recovery of her liver cells. The probable importance of vitamins in these cases, and specifically of vitamin C, is generally agreed upon. Although there is some experimental evidence that cortisone inhibits regeneration of liver parenchyma in the rat,[13] and that it enhances cirrhosis in rats exposed

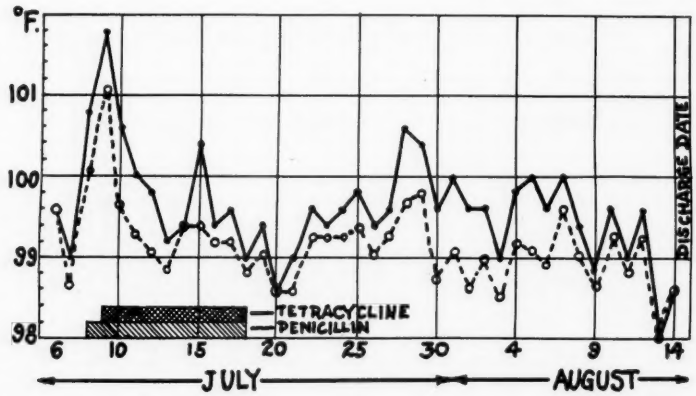

FIG. 3. Oral temperature chart. Daily maximum reading ——. Daily average reading ----.

to carbon tetrachloride vapors,[3] it was felt that the well substantiated choleretic action of cortisone gave one reason for its use in this case. Patterson et al.[12] demonstrated recently that cortisone, both intravenously administered and duodenally instilled, caused a consistent increase in the volume (hydrocholeresis) and the concentration (choleresis) of bile salts and pigment in aspirated duodenal contents. That this increase in bile flow was not due to contraction of the gallbladder was demonstrated by eliciting similar responses in cholecystectomized patients. The cortisone-induced increase in bile flow is thought to produce a "filtering-off" of the excess serum bilirubin.

The problem of the patient's agranulocytosis merits consideration. Agranulocytosis was first reported as a clinical entity by Schultz in 1922. Because of the severity of this condition, a large number of drugs have been used in an attempt to stimulate granulocytopoiesis. The popularity of the various nucleic acid derivatives has in recent years given way to that of cortisone and ACTH. There is an abundance of literature about the beneficial effects of the steroids in cases of drug-induced or other types of agranulocytosis.[1, 18,19] Whether cortisone actually accelerated the rate of recovery of our patient's marrow is

a moot question. In severe cases found in the literature with a comparable lowering of the white blood cell count, there seemed to be an elapsed period of seven or eight days before the white count returned to normal or higher, despite the fact that no steroid therapy was given.[11, 14, 16] Cases treated with cortisone or ACTH required a similar lapse of time before apparent recovery of granulocy-

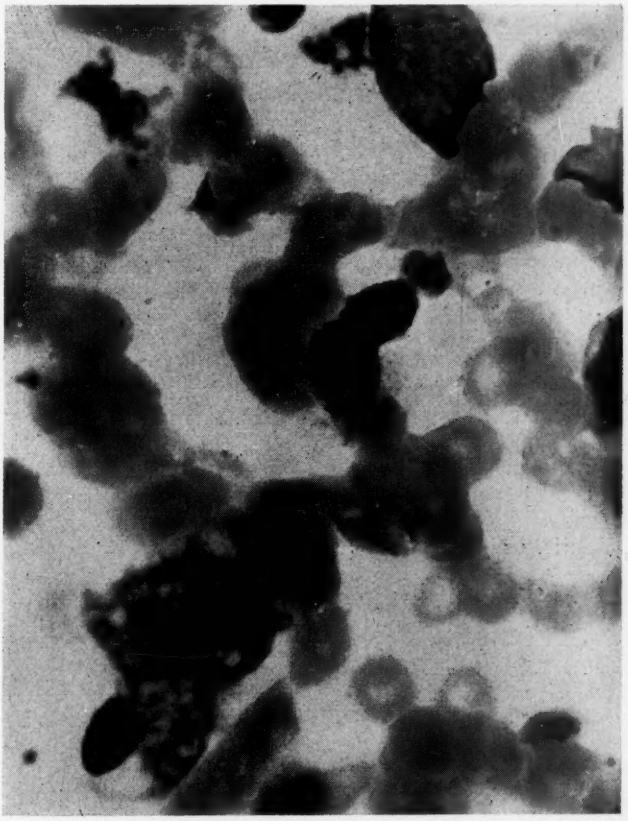

FIG. 4. Photomicrograph of sternal marrow (Wright's stain, × 1200). Lipoid histiocyte in lower left quadrant. Note absence of granulocytic series.

topoiesis.[1, 18] Included in this latter group, of course, is the present case. The "overshooting" of the rebounding white blood cells, as observed in our patient, was seen commonly in similar cases in the literature.[1, 11, 18]

The necessity of prophylactic antibiotic administration in cases of agranulocytosis is well recognized. Saler [15] reports a very high mortality rate in untreated cases, and proposes a prophylactic regimen consisting primarily of penicillin and a wide-spectrum antibiotic. Our patient's mild hospital course and fall in temperature were, we believe, at least partly due to the antibiotic therapy which she was given during her granulocytopenia (figure 3).

A noteworthy feature of this patient's agranulocytosis is the fact that the eosinophils in her bone marrow were not reduced from their normal numbers, although there was a marked decrease of other granulocytes and granulocytic precursors. This finding may lend additional weight to the theory proposed by Essellier et al.[4] that the eosinophil-cell system is independent of the neutrophils in cases of agranulocytosis. In 53 cases of agranulocytosis observed between 1929 and 1951, these investigators found that there were 11 cases in which there was "a persistence of eosinophiles or even a definite eosinophilia appearing during the agranulocytosis." That this eosinophilia cannot be interpreted as an allergic reaction is made clear in their report. The independence of the non-granulocytic white cells, the red cells and the platelets, is a well known phenomenon and is convincingly shown in our patient.

An interesting and somewhat enigmatic observation in the bone marrow study was the frequent occurrence of lipoid histiocytes (figure 4). These were large reticuloendothelial cells filled with fat, which were thought to represent a severe disturbance of lipid metabolism due, in this particular case, to liver damage of considerable extent. The stimulation by lipids of monocytic proliferation has been suggested elsewhere.[20] The puzzling aspect here lies in the fact that one might tend to predict a high serum cholesterol on the basis of this finding; our patient, however, had a total serum cholesterol of only 139 mg. %, with 77% esters.

Although the question was briefly raised whether the skin rash which developed on the patient on her sixteenth hospital day was another manifestation of cinchophen sensitivity, the timing of the onset and the character of the eruption led us to the conclusion that it was not related to cinchophen. Hueper[8] describes the cutaneous reaction to this drug as taking the form usually "of itching, purpuric, urticarial, or scarlatiniform eruptions, or of exfoliative erythroderma, —— sometimes associated with angioneurotic edema." Zubrod,[22] Short and Bauer[17] and Lenzer et al.[10] report vesicular and urticarial lesions as being more characteristic of the reaction to cinchophen than the macular and subsequently confluent dermatitis exhibited in our patient. It was thought consequently that this rash may have represented an allergic response to penicillin.

The appearance of a trace of albumin in one of this patient's urinalyses was not thought to be sufficient evidence of any renal reaction to cinchophen, even though various investigators[7, 10] have reported albuminuria and kidney damage in cinchophen poisoning. It is possible that tubular damage associated with the high level of bilirubinemia was responsible for this occurrence.

Summary and Conclusions

A case has been presented of toxic hepatitis and agranulocytosis following and possibly due to cinchophen sensitivity. Attention has been called to the severity of the jaundice, the therapeutic measures employed, and the effect of cortisone in such conditions. It has also been noted that the return of granulocytopoiesis in this case was apparently not significantly accelerated by cortisone. The alleged independence of the eosinophils in cases of agranulocytosis has also been demonstrated by our findings. A reinforcement of the oft-voiced warning

about the dangerous side-effects of cinchophen, even though it may have been previously administered with impunity, is inherent in this report.

Summario in Interlingua

Isto es un reporto de un feminina blanc de 59 annos de etate qui esseva admittite al hospital a causa de sever jalnessa, anorexia, e malaise de septe a 10 dies de duration. Immediatemente ante le declaration del symptomas illa habeva usate un prescription pro arthritis que contineva 0,5 g de cinchophen in omne dose. Iste droga esseva administrate omne quatro horas durante 10 dies ante le declaration del symptomas. Le numeration leucocytic al tempore del admission al hospital esseva 800 e se teneva vicin a 1.000 cellulas per cm^3 durante un septimana. Postea illo cresceva e attingeva 19.400 duo septimanas post le hospitalisation. Plus tarde le numeration leucocytic retornava a nivellos normal.

Studios de function hepatic confirmava le impression de un sever insulto hepatocellular. A causa del augmento initial de bilirubina e de sever grados de anorexia, alimentation intravenose con 10 pro cento de glucosa esseva instituite. Cortisona esseva administrate per via oral ab le tertie usque al vinti-quarte die hospitalari. Al tempore del dimission ab le hospital, sex septimanas post le admission, le bilirubina del sero habeva retornate a nivellos quasi normal, e le patiente experientiava un complete restablimento symptomatic e clinic.

Examines de medulla ossee, effectuate le die post le admission del patiente al hospital, demonstrava un quasi complete absentia de cellulas del serie granulocytic, excepte le eosinophilos e lor precursores. Elementos erythroide e megakaryocytos esseva presente in numeros normal.

Es opinate que le insulto hepatocellular e le agranulocytosis exhibite per iste patiente esseva le resultato de un reaction toxic al cinchophen administrate durante 10 dies ante le declaration del symptomas. Le facto que le patiente habeva recipite cinchophen sex annos ante le maladia hic reportate non es un argumento contra le incrimination del droga, proque le mesme typo de reaction a cinchophen ha essite reportate per altere autores.

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A REVIEW OF THE RELATIONSHIP BETWEEN PREGNANCY AND PORPHYRIA AND PRESENTATION OF A CASE*

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There have been a number of scattered reports of pregnancy in porphyric women and the various problems which attend this condition. To our knowledge, there has been no review of these experiences which would serve as a touchstone to others who encounter such gestation.

Porphyria is more commonly thought of and detected today in clinical medicine. Complicating circumstances such as pregnancy will be seen more frequently. Problems arise in its management which cannot be solved solely on a physiologic basis, since the nature of the interplay between the fetal and maternal factors is unknown. Although the intricacies of porphyrin metabolism have been greatly clarified, bedside management is generally supportive and empiric.

This review will summarize and attempt to analyze such experience as has been reported. In addition, a case recently observed will be presented to illustrate the difficulties of the problem.

Case Report

A 22 year old white married female secretary was admitted on May 22, 1955, complaining of inability to extend her fingers for the last three weeks. She had no pain, paresthesia or weakness in other muscle groups.

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Her last menstrual period had been 58 days before. She had been married five months previously, and had had tender breasts and nausea for about three weeks.

Past History: The patient had been "on the verge of a nervous breakdown" several times in the last few years. Two years before, after a beau had been killed in an automobile accident, she had had fever followed by arthralgia which had been diagnosed as rheumatic fever by her local physician. She was treated with bed-rest for two months. She had had no antecedent sore throat, no murmurs or other objective evidence of rheumatic fever or heart disease.

She had had some abdominal pain in the past, but no details were available. She had had low back pain for about five years and constipation for two years, without other symptoms of bowel disease. The patient had received unknown amounts of barbiturates in the few weeks before admission to the hospital.

Physical Examination: The patient was a thin well developed white female who appeared to be very anxious. Her voice had a whining quality. Blood pressure was 100/65 mm. of Hg; pulse, 120 and regular; respiration, 18; temperature, normal. Examinations of ears, nose and throat were negative. Fundi were normal. The neck was normal. There were no enlarged nodes. The heart was not enlarged. Sounds were good. There were no murmurs. The lungs were clear to auscultation and percussion. Abdominal examination was normal. Extremities were negative. The fingers were flexed at the proximal joints and could not be actively extended past a midposition. The mobility was normal passively. There were no pathologic reflexes. Sensory examination was normal. Deep tendon reflexes were as follows: radial jerks, 0; ulnar jerks, 0; biceps jerks, 2 plus; triceps jerks, 1 plus; abdominals (superficial), 2 plus; knee jerks, 0; ankle jerks, 0.

The uterus was enlarged to the size of a six week gestation. The cervix was soft and bluish.

Admission laboratory examinations were as follows: hemoglobin, 11.1 gm.; red blood cells, 3.4 million; white blood cells, 13,188; neutrophils, 66; lymphocytes, 30; monocytes, 3; eosinophils, 1. Urinalysis, negative. Sedimentation rate, 18 mm. in 1 hour. Kolmer and VDRL, negative. C reactive protein, negative. Fasting blood sugar, 86. Blood urea nitrogen, 11.8. Serum bilirubin, 0.6 mg. Serum cholesterol, 227 mg. %. Serum cholesterol esters, 82 mg. %. Serum alkaline phosphatase, 3.1 units. Serum protein, 6.2 mg. %. Albumin, 4.9. Globulin, 1.3. Bromsulphalein, 36% in 30 minutes (5 mg. per kilogram). Cephalin flocculation, 2 plus in 48 hrs. X-rays of the chest and cervical spine were normal.

The electrocardiogram showed sinus tachycardia. A lumbar puncture was done and manometric measurements were normal. The fluid was crystal clear. There were 8 cells per cubic millimeter (7 lymphocytes, 1 polymorphonuclear). The protein was 27 mg. %.

Course in Hospital: For the first week in the hospital the chief problem in diagnosis was to determine whether the patient had organic nervous disease or whether all her complaints were hysterical. She complained bitterly of abdominal pain but when her attention was distracted she did not seem to be bothered by pain. She created a disturbance by crying out for her husband, and appeared to be disoriented at times. These manifestations and the past history of mental instability made the diagnosis of hysteria a tempting one.

However, at the end of the first week her weakness had extended to involve the wrist and, to a lesser extent, the shoulder girdle. It was felt that this was a motor peripheral neuropathy and, on this basis, a urine determination of porphyrins was ordered.

In the 24 hour urine specimen the uroporphyrin was 46.17 mg. and the coproporphyrin was 3172 μg. At this time the family history was further investigated and it was found that two uncles had died with a paralytic disease that had apparently

started in their hands. Urine from her mother showed a positive test for porphyrins. Urines from two sisters and several nieces were negative for porphyrins.

On the eleventh hospital day the patient had definite weakness in the legs. She was started on Meticorten by mouth, 5 mg. four times a day.

On the thirteenth hospital day the patient's voice became very weak and she spoke in a whisper. She was unable to swallow. Her tongue was deviated to the left. There was no pharyngeal reflex, and her external ocular movements were discoördinated. Intravenous ACTH was started. The following day the patient began to have great difficulty in breathing. There was very little motion of the chest. She was therefore put in the respirator. The ACTH was raised to 80 units a day, and potassium chloride was given in the infusion. She made slight improvement in the strength of her legs in the following week. Because it was difficult to maintain her on intravenous fluids, a plastic nasogastric tube was inserted and she was given tube feedings.

There was no change in her general or neurologic condition. Breath sounds were diminished over the right anterior upper chest.

Other medications given were vitamin B_{12}, 1,000 μg. a day intramuscularly, paraldehyde for restlessness and codeine for leg pains. Intramuscular ACTH was substituted for the intravenous, 25 mg. every eight hours. Cortisone was given, 50 mg. every eight hours intramuscularly.

On the fiftieth hospital day the patient had a spontaneous abortion of an 8 ounce fetus and a 10 cm. placenta. There was no remarkable change until the fifty-seventh hospital day. From this time until she died on the sixty-third hospital day she gradually became generally weaker. As the nurse was turning her, she suddenly stopped breathing and was declared dead.

Pathologic Findings

External Examination: The body was that of a young white woman. She was extremely emaciated, but otherwise the external examination was not remarkable.

Internal Examination:

Pleural cavities: Each pleural cavity contained approximately 700 c.c. of clear yellow fluid.

Pericardial cavity: Negative.

Peritoneal cavity: Negative.

Neck: The thyroid was grossly normal in shape, size and consistency.

Lungs: The right lung showed a moderate fibrous adhesion between the upper lobe and the parietal pleura. The lungs together weighed 825 gm. Both lower lobes were moderately atelectatic. The right upper lobe was a dark reddish purple in color, and cut section showed a grayish red surface with many confluent, white, dryish areas indicating pneumonitis. This appeared to be a lobar pneumonia but conceivably could have been a confluent lobular pneumonia. The bronchi contained a moderate amount of mucus, and the mucosa was somewhat reddened. The pulmonary vessels were free of emboli.

Heart and Aorta: The heart weighed 300 gm. It was small, somewhat flabby and dark red. No other abnormalities were noted. The aorta was free of atheromatous parts.

Liver and Biliary Systems: The liver weighed 1,450 gm. and was dark red and smooth.

Gall-bladder: The gall-bladder was small and free of stones. Bile could be expressed freely through the ampulla.

Pancreas: The pancreas was normal in size and shape.

Spleen: The spleen weighed 150 gm. and was slightly enlarged, dark red and moderately firm.

Kidneys and Ureters: The kidneys weighed 165 gm. each. The capsule stripped with ease. No gross abnormality was recognized.

Adrenal Glands: The adrenal glands were larger than normal and the cortex was definitely thickened. It was moderately yellow. Each adrenal gland weighed 14 gm. Grossly they were approximately twice the size which might be expected in a patient of this size. This was considered attributable to the ACTH, which the patient had received.

Bladder: Negative.

Gastrointestinal Tract: The gastrointestinal tract was essentially negative except for a dilated segment of transverse colon, which extended approximately 12 cm. along the colon. At either end the bowel was constricted.

Genitourinary Tract: Essentially normal.

Bone Marrow: The bone marrow was dark red.

Skull, Brain and Spinal Cord: The brain and the entire spinal cord were removed. They were grossly normal. Segments of nerve from the brachial plexis were also removed for histologic examination.

Microscopic Description: Thyroid: The acini were moderate in size, lined by flattened cells or cuboidal cells, and full of pink-staining colloid. Sections were interpreted as normal. *Heart:* Sections of heart muscle appeared normal. *Lung:* Sections of lung showed foci where many alveoli were filled with neutrophils. In some areas the alveolar walls could not be seen, which suggested necrosis and early abscess formation. These areas shaded out into normal lung, indicating that the patient had had a confluent bronchopneumonia rather than a lobar pneumonia. *Liver:* The general structure was maintained. The sinusoids were somewhat distended. There was a moderate degree of fat vacuolization. Kupffer cells showed considerable deposition of granular brown pigment, interpreted as hemosiderin. *Pancreas:* The general structure was maintained. No abnormality was recognized in the islets. There were scattered small patches of fibrosis and mild lymphocytic infiltration; these were interpreted as indicating a mild, diffuse chronic pancreatitis. *Spleen:* Congestion. *Adrenals:* The cortex was very thick. The cells contained a moderate amount of lipoid. *Kidneys:* Normal. *Bone Marrow:* The bone marrow was moderately filled. There was a fair number of foci of nucleated red cells. Young granulocytes were increased in number. The marrow appeared to show simple granulocytic hyperplasia. The reticuloendothelial cells showed mild hemosiderin deposition.

Nervous Tissue: The most severe alterations were seen in the peripheral nerves. Here the myelin had completely degenerated and was undergoing swelling and fragmentation. The axis cylinder was also undergoing degeneration, many fibers being completely absent, and in other areas appearing swollen and staining poorly. In the peripheral nerves the endoneural collagen appeared to be increased. Schwann's cells were not increased in number but in some areas were swollen. Occasional macrophages were noted.

Demyelinization was also noted in both sensory and motor roots at all levels of the spinal cord and in the extramedullary fibers of the tenth and twelfth nerves.

The central nervous system showed rather widespread decrease in neurones, especially in the supragranular layers of the cortex and in the dentate, pallidum and inferior olive. This was associated with a moderate increase in astroglia, especially in the dentate and olive. These were nonspecific changes and may have been related to anoxia or nutritional deficiency.

In the spinal cord the anterior horn cells were definitely decreased in the cervical region. This involved the medial groups particularly, and was associated with a mild astroglial proliferation. No alteration was noted in the Betz's cells of the motor cortex.

Pathologic Diagnosis: Lobar pneumonia, right upper lobe; basilar atelectasis,

both lower lobes; severe emaciation; adrenal hyperplasia; intermittent porphyria; peripheral neuropathy (due to porphyria).

Discussion

We were able to collect reports of 27 pregnancies in 16 women with porphyria. Those cases with insufficient data or follow-up were excluded. The porphyria was of the acute intermittent or mixed type in all cases.

Five women in this series had had multiple pregnancies. One woman had been pregnant seven times.[1] Her initial pregnancy went to full term. The other six pregnancies terminated in early, spontaneous abortion. With each pregnancy there were clinical exacerbations of the porphyria. Two women were each pregnant three times.[2] In the first of these women the porphyria became worse with each pregnancy. In the second woman the first pregnancy was normal and full term. The second ended in spontaneous abortion at four months, without maternal distress, and the third was reported up to three months,

Table 1

27 Pregnancies in 16 Women with Porphyria

	Full Term	Spontaneous Abortion	Surgical Term	Unknown
Eventual course of pregnancy	12	9 (6 episodes in 1 patient)	3	3

	Improvement	Exacerbation	No Change
Effect of pregnancy upon the clinical state of porphyria	2	21 (7 episodes in 1 patient)	4

Mortality: 4 Deaths—26%.

during which time there were no unusual findings. Two women were each pregnant twice.[3, 4] In one of these women the porphyria was aggravated during each pregnancy. In the other woman the porphyria was undetected and asymptomatic during the initial pregnancy. During the second pregnancy she spontaneously aborted at two months and died shortly thereafter. The remaining 11 women had histories of single pregnancies. In nine of these there was exacerbation of the porphyria during pregnancy,[5, 6, 7, 8, 9, 10] with one death recorded. In two of these patients hysterotomy was done. Both of these women died, one six days after operation;[8] the other had a short remission of six weeks and then developed respiratory paralysis and died.[9] Spontaneous abortion occurred in several women in this group with single pregnancies. In only two women was there a suggestion of a favorable effect of pregnancy on the porphyria.[11, 12]

This review indicates that there is a decided tendency for porphyria to undergo exacerbation during pregnancy. However, it must be remembered that the cases reported may have been selected because of unusual circumstances. There would be less tendency to report cases of porphyria with uncomplicated pregnancy. It is interesting that, in nine of the 16 women, the diagnosis of

porphyria was made for the first time during pregnancy. This does not mean that clinical symptoms or signs first became apparent then. Review of histories indicated that in most of these women there were previously unexplained illnesses which were probably of porphyric origin. However, this does suggest that the severity of the clinical state during pregnancy was such as to warrant thorough investigative studies in these patients. There were four deaths in the series. Two of these deaths, as previously mentioned, occurred following hysterotomy. Two other deaths occurred shortly after spontaneous abortion and were associated with respiratory paralysis.

The cause of the exacerbation in the clinical manifestations of porphyria during pregnancy is unknown. Some observers have suggested that the use of sedatives in early pregnancy, where the diagnosis of porphyria is unsuspected, or where the attending physician is unaware of the noxious influence of these drugs, is perhaps responsible. This seems a possible explanation in isolated cases. However, we doubt if it explains the phenomena in the entire group. In those cases which were artificially terminated there was apparent aggravation in each instance. Perhaps in this situation the use of an anesthetic or sedative prior to the operative procedure was the triggering factor. If this is not the case, it would appear that therapeutic abortion may be as detrimental as the pregnancy itself and cannot be recommended in the light of present experience.

It should be added that several cases were reported in which curettage had been done with apparent benefit. However, these cases are either insufficiently documented or lacked reasonable follow-up.

We are not attempting in this paper to define the effects on the fetus or the newborn, because these findings were not available in the papers that were reviewed. However, in those pregnancies going to term it appeared that the infant was as normal at birth as would be expected in the general population. We know that the genetic basis for the inheritance of porphyria predisposes the infant to eventual development of this disease.

Summary

1. In the cases reported, pregnancy has shown a decided tendency to exacerbate the clinical state of porphyria. No doubt there have been many unreported cases of pregnancy with a benign course.

2. The status of therapeutic abortion during exacerbation is unsettled. It is possible that it may be of benefit if sedatives or anesthetic agents known to be harmful could be omitted.

3. The clinical manifestations of porphyria have been reviewed in many previous papers. In summary, any patient with bizarre pain, peripheral nerve disease (especially weakness), or neurotic or psychotic episodes should be suspect for this disease. Reddish urine is particularly important. The diagnosis can be made by determination of porphyrins in the urine.

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SUMMARIO IN INTERLINGUA

Un pregnante femina blanc de 22 annos de etate moriva con le manifestationes de porphyria in su systema nervose. Le historia clinic e le constatationes microscopic es presentate.

Le litteratura reporta 27 pregnantias in 15 feminas con porphyria. In 9 del 15 feminas, le diagnose de porphyria esseva facite le prime vice durante un pregnantia. Iste casos esseva analysate, e le sequente conclusiones esseva formulate:

1. Pregnantias ha un decidite tendentia a exacerbar le stato clinic de porphyria. Non es a dubitar que multe casos ha occurrite in pregnantias con curso benigne que non pareva digne de reporto.

2. Le causa del exacerbation que occurre in le manifestationes clinic de porphyria durante un pregnantia non es cognoscite. Certe observatores opina que le uso de sedativos durante le prime phases del pregnantia—in casos ubi le diagnose de porphyria non es suspicite o ubi le medico non es conscie del influentia nocive de iste drogas—es possibilemente a blasmar. Iste explication pare possibile in casos individual. Sed nos non crede que le phenomeno pote esser explicate assi in le gruppo integre. In le casos in que un termination artificial esseva effectuate, aggravation del condition esseva invariabilemente apparente. Il es possibile que in iste casos le uso de un anesthetico o un sedativo ante le intervention operatori esseva le factor precipitante. Si isto non es le caso, il pare que aborto therapeutic es non minus detrimentose que le pregnantia mesme. In le lumine del presente cognoscentias, aborto therapeutic sub iste conditiones non pote esser recommendate.

3. Multe previe publicationes ha presentate revistas del manifestationes clinic de porphyria. In summario, omne patiente con bizarre formas de dolor, con morbo de nervos peripheric (e specialmente debilitate) o con episodios neurotic o psychotic debe esser considerate como suspecte. Urina de color rubiastre es particularmente importante. Le diagnose pote esser establite per le determination de porphyrinas in le urina.

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EDITORIAL

THE VALUE OF DETERMINATIONS OF CHOLESTEROL AND OF LIPOPROTEINS OF LOW DENSITY IN THE BLOOD AS PREDICTORS OF OVERT ATHEROSCLEROSIS

THE increasing importance of atherosclerosis as a cause of death has intensified interest in this serious disturbance and stimulated extensive investigations. One major phase of this subject now under active study and debate is the relationship of cholesterol and other lipids to atherosclerosis, both as a possible causative factor and as an indicator or predictor of existing or impending disease.

In patients with ordinary atherosclerosis a high concentration of cholesterol is found in many individuals, and levels significantly above normal have been reported in many studies of such groups. Some of the earlier reports we have previously reviewed here.[1] There are so many individual exceptions, however, that factors other than a high blood cholesterol must also be concerned.

Gofman and his associates [2] have pointed out that cholesterol does not circulate in the blood as such but in combination with protein, as "giant" lipoprotein molecules of low density (beta lipoproteins). If the specific gravity of the serum is suitably increased by the addition of salt, and it is then subjected to ultracentrifugalization for many hours, these lipoproteins will float toward the surface. Their segregation in the upper layers of the fluid results in proportionate changes in optical density (refractivity) so that quantitative estimates can be made by appropriate photographic procedures. Several more or less arbitrarily delimited fractions can be differentiated, according to the speed of their flotation. Gofman has distinguished four such groups (S_f 0–10 (or 12), S_f 12–20, S_f 20–100, and S_f 100–400; the higher the numeral, the lower the density). These fractions are stated to differ in other respects, including their cholesterol content and in the apparent closeness of their relationship to atherosclerosis.

If the cholesterol in the blood is combined with protein, the hypothesis advanced by Gofman seemed reasonable, that any relationship to atherosclerosis that may exist depends upon the lipoprotein molecule as a whole and not merely on the cholesterol fraction. To test this Gofman and his associates carried out extensive studies of patients with definite evidence of a myocardial infarction (or later, also, of angina pectoris [3, 4]), comparing

[1] Editorial: The relation of cholesterol to the development of atherosclerosis, Ann. Int. Med. **33**: 250–258, 1950.

[2] Gofman, J. W., et al.: The role of lipids and lipoproteins in atherosclerosis, Science **111**: 166–171, 1950.

[3] Gofman, J. W., et al.: Blood lipids and human atherosclerosis, Circulation **2**: 161–178, 1950.

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them with apparently normal control subjects from the same base population from which the patients sprang. In numerous reports [5] they published figures indicating that the average concentration of these lipoproteins of low density or of certain fractions of them was significantly higher in subjects with manifest atherosclerosis. They also claimed that the correlation of atherosclerosis with a high level of lipoproteins was much closer than with a high cholesterol level. This they attributed in part to differences in the percentage of cholesterol contained in the various fractions of the lipoproteins.

The technic of these ultracentrifugal analyses is unusually complicated and requires a competent team of highly trained technicians in constant practice to get reliable and reproducible results. It requires costly apparatus which is difficult and expensive to operate and to maintain. Partly for these reasons, perhaps, earlier attempts to confirm these findings in other laboratories were largely unsuccessful, and much controversy arose over the value of the procedure. The importance of deciding the question is obvious.

In order adequately to investigate this matter as well as other related problems regarding atherosclerosis, a coöperative study was undertaken under the supervision of the National Heart Council by four groups of investigators, in the Donner Laboratory of the University of California, the Cleveland Clinic Foundation, the University of Pittsburgh, and the Harvard School of Public Health. This was a prospective study, in which great pains were taken to avoid bias, particularly in the selection of subjects and in the interpretation of "new events" indicating the onset of overt coronary arterial disease. For details as to these precautions the reader is referred to their report.[6]

In an effort to make the data from the different groups comparable, great care was taken and much sustained effort required to insure uniform technic and accurate and reproducible results in the different laboratories. At first even in the relatively simple cholesterol determinations, "intolerable differences" were demonstrated; and in the liprotein determinations, at one time, erroneous results were discovered (and discarded) even in the Donner Laboratory because of some mechanical defect in the centrifuge cells which was not immediately recognized. Even so, indiscriminate pooling of the figures was impracticable. The recent report covers merely the observations on the lipoproteins and the total blood cholesterol and their relation to developing overt atherosclerosis.

From a base population of 4914 males from 40 to 69 years of age, clinically "normal" at the start of the period of observation of one to two years,

[5] Gofman, J. W., et al.: Lipoproteins, coronary heart disease and atherosclerosis, Physiol. Rev. **34**: 589–607, 1954.

[6] Gofman, J. W., et al. (Technical Group), Andrus, E. C., et al. (Committee on lipoproteins, etc.): Evaluation of serum lipoprotein and cholesterol measurements as predictors of clinical complications of atherosclerosis, Circulation **14**: 691–741, 1956.

82 developed signs of "new disease," in 65 attributable "definitely" and in 17 probably or possibly to coronary atherosclerosis, in the opinion of a Review Committee who were not aware of the results of the chemical studies. The data from the four laboratories were reported to a central statistical office before the results of the follow up of the subjects were known. Here they were subjected to a critical analysis by various statistical procedures.

A detailed discussion of this mathematical treatment is not feasible in a review of this sort, but the conclusions reached from the figures supplied by the coöperative group as a whole may be summarized quite succinctly. A comparison of the mean values of the various lipid fractions shows higher figures for the subjects suffering new events than for the base population; statistically "highly significant" for cholesterol, not definitely so for the lipoprotein fractions. Similarly, if the median (fiftieth percentile) point of each of the lipid fractions is determined for the base population and the corresponding figures for subjects suffering new events are compared with them, in a majority of the diseased subjects the value of each fraction will fall above the median point. The difference was highly significant for cholesterol, definitely so for the S_f 20–100 lipoprotein, but not statistically significant for the S_f 12–20 fraction.

As to the relative ability of these determinations to predict new events, the differences were not very great, but cholesterol was found somewhat superior to the S_f 20–100 and notably better than the S_f 12–20 lipoproteins.

Gofman and the Donner Laboratory group have taken vigorous exception to some of these conclusions, particularly the latter. At the onset of the study the ultracentrifugal analysis of the lipoproteins was a relatively new procedure, and as experience was acquired the Donner group suggested several refinements and extensions of the procedure which they thought accentuated the differences between the normal and diseased subjects.

These included separate measurements of additional groups of lipoproteins, some of which were generally adopted as feasible and carried out. Others, such as a correction for slowing of the flotation in sera with high concentrations of lipoprotein,[7] and the calculation of an "atherogenic index" [8] to allow for apparent differences in the relative significance of various fractions of the lipoproteins were not acceptable; some because it was not feasible for the Eastern Laboratories to make the changes after the bulk of the work had been completed or because it involved a late change in the original plan of the study which they thought was unwarranted, and some because they were regarded as statistically unsound.

The Donner group also objected to the exclusion by the Review Com-

[7] Gofman, J. W., et al.: Blood lipids and human atherosclerosis, Circulation **5**: 119–134, 1952.

[8] Gofman, J. W., et al.: Index of coronary artery atherogenesis, Mod. Med. **11**: 119–140, 1953.

mittee of 24 subjects with supposedly new events because further study (before the results of the chemical tests were known) showed that these were abnormal at the start. The Donner group also wished to drop from consideration those whose new event was angina pectoris or some other manifestation of atherosclerosis less definite than a myocardial infarction. Since this was suggested after the results of the study were known, it would have introduced an unpermissible form of statistical bias. If these various modifications had been acceptable, the figures for the S_f lipoproteins would have made a relatively better showing. This, however, is really more a matter of emphasis and degree than a fundamental divergence.

The results do show, *on the average,* higher concentrations of all three lipid fractions in those subjects who later suffered definite "new events" than in those who did not. The figures are statistically significant, except perhaps for the S_f 12–20 fraction. They prove that the increase antedates the actual infarction and is not a result of it, and to that extent they have some limited predictive value. This is not true, however, for individual subjects. The overlap is very large, the difference between individuals in the same group is often greater than the difference between the averages of the two groups. For practical purposes, therefore, these determinations had no value in predicting whether a given individual would develop an overt attack during the period of observation of one to two years.

This point is further emphasized in the report of the Coöperative Study by pointing out that, on the basis of this experiment, from 1000 "normal" males 40 to 59 years of age, 20 would be expected to develop a new event during the two year period. If the anticipated lipoid figures of these 20 subjects are compared with the median figures of the normal group, not over 14 would be expected to fall into the upper half and not less than six (false negatives) into the lower half. With the 14 valid positive predictions, however, about 500 normal subjects will show similarly high figures, false positives.

Even if the period of observation were protracted to 20 years, and if we may assume that the rate of development of atherosclerotic accidents remained the same, there should still be three to four false positives for each true prediction, from a practical standpoint an intolerable discrepancy.

It seems on the whole fortunate from the standpoint of simplicity and economy that the determination of cholesterol had as great predictive value as that of the lipoproteins. Determination of the latter is doubtless a valuable research tool, but with present technic it is too costly and unwieldy to be usable in the average hospital laboratory. Recent advertisements of commercial laboratories making claims to the contrary are entirely unwarranted and misleading.

The general conclusions of the majority of those participating in the coöperative study have recently received some further confirmation. Lawry

et al.,[9] who participated in the coöperative study, reached similar conclusions on the basis of a comparison (not a prospective study) of 1968 "normal" adults, 273 men and 23 women with evidence of definite myocardial infarction and 141 men with angina pectoris. Doyle et al.[10] from the New York State Health Department and the Albany Medical College reached similar conclusions after a study of 115 white male office workers; 76 free from ischemic heart disease, 28 survivors of a myocardial infarction, and 20 with angina pectoris. The subjects with infarction showed higher average figures for the lipoprotein fractions, but the authors conclude that the current technics are "neither qualitatively nor quantitatively satisfactory indices of atherogenicity in a homogeneous population highly susceptible to ischemic heart disease." They also conclude "that the serum total cholesterol provides as much (or as little) information as more elaborate and difficult chemical procedures."

Although in a given subject a high figure for blood lipids has little value in predicting a serious coronary arterial lesion, it may prove to have more significance as an indication of atherosclerosis in general. In males 40 to 60, previous autopsy studies have shown a high incidence of unsuspected atherosclerosis. The basic group in this study, perhaps, might better be called "symptomless" than "normal." A really normal control group might be available only in much younger subjects or in other races or nationalities, perhaps with different habits of eating, like the rural (vegetarian) Guatemalans,[11] the Japanese, or the South African native Negro races, who are reported to have low blood cholesterol and reputedly less atherosclerosis.[12]

The part played by the fat content and caloric value of the diet and by obesity per se in altering the concentration of the blood lipids and in the development of atherosclerosis is manifestly a problem of great importance, as is also the possibility of controlling this by dietary measures. These questions are under active investigation, among others by those participating in the Coöperative Study. This part of the study was not included in their recent report, and it will not be discussed here. In the meantime, as Page succinctly expressed it,[12] "unless they feel the need of one, physicians need no longer develop cardiac neuroses from contemplation of some minor variation in their serum lipoprotein pattern."

PAUL W. CLOUGH

[9] Lawry, E. Y., et al.: Cholesterol and beta lipoproteins in the serum of Americans, well persons and those with coronary heart disease, Am. J. Med. **22**: 605–623, 1957.

[10] Doyle, J. T., et al.: Serum proteins in preclinical and in manifest ischemic heart disease, J. Chronic Dis. **6**: 33–46, 1957.

[11] Mann, G. V., et al.: The serum lipoproteins and cholesterol concentration of Central and North Americans with different dietary habits, Am. J. Med. **19**: 25, 1956.

[12] Page, I. H.: Predictive value of lipoprotein measurements in coronary atherosclerosis, J. A. M. A. **163**: 454–455, 1957 (Guest editorial).

REVIEWS

Pathologic Physiology: Mechanisms of Disease. 2nd Ed. Edited by WILLIAM A. SODEMAN, M.D., F.A.C.P., Professor of Medicine, School of Medicine, University of Missouri. 963 pages; 17 × 25.5 cm. W. B. Saunders Co., Philadelphia. 1956. Price, $13.00.

The second edition of this popular text has been considerably enlarged with revisions of previous chapters and the addition of three new chapters. A new chapter on Neurology bridges a gap which existed in the previous volume, and another chapter extends the earlier discussion of carbohydrate metabolism. A third new chapter is a masterful summary of the present status of research into the genetic bases of cancer, and also contains much information to enable the student and practitioner to evaluate critically results of future research in that field and in the field of developmental anomalies.

G. E.

Heart Sounds, Cardiac Pulsations, and Coronary Disease. By WILLIAM DOCK, M.D., Professor of Medicine, State University of New York, College of Medicine at New York City. 98 pages; 14 × 21.5 cm. University of Kansas Press, Lawrence. 1956. Price, $2.50.

In this book are included the Porter Lectures as given by the author in 1955 at the University of Kansas. In the first chapter, "The Clinical Significance of Pulsations Evoked by the Heartbeat," the author discusses the venous pulse, arterial pulse, cardiac pulses, the ballistocardiogram, and various technics of recording the ballistocardiogram. He evaluates the ballistocardiogram in health and disease and states, "In our experience, the traces of the big pulse have not been harmful to any patient, and they were helpful in demonstrating to some that smoking affected their hearts adversely and to others that the pumping function of the heart was unaffected by old or recent myocardial infarction."

The second lecture, "The Production of Sounds by Normal and Diseased Hearts," is a discussion of the history of auscultation and the mechanism of sound production. In the third, "Coronary Disease—The Professor's Friend," is contained a history of coronary artery disease and a discussion of the relationship of atherosclerosis and coronary disease. This book is recommended reading for medical students and physicians. In it are contained the interesting and at times provocative opinions of the author presented in an extremely readable manner.

L. S.

Radiology of the Heart and Great Vessels. By ROBERT N. COOLEY, M.D., and ROBERT D. SLOAN, M.D. 309 pages; 20 × 27.5 cm. The Williams & Wilkins Co., Baltimore. 1956. Price, $12.00.

Accurate anatomic diagnosis in cardiology, always important for the care of the cardiac patient, becomes more critical as technics in cardiac surgery improve. As in other disciplines, new radiologic methods for more precise study of the cardiovascular system have been developed. Dr. Cooley and Dr. Sloan have produced a fine book extensively covering radiologic features of the heart and great vessels.

The sections discussing technics are especially rewarding. Methods of angiocardiography and the associated hazards receive considerable emphasis. All reported fatal reactions following angiocardiography are analyzed. This procedure enjoys a favored position in the book, and in the authors' hands seems a safe and extremely

valuable tool. The initial cost of equipment and special training period required to master the technics will limit its use to large medical centers. However, knowledge gained from use of angiograms can be used in the interpretation of conventional films, provided reasonable precautions are taken in transposition of this information.

Normal roentgenologic patterns are covered. The bulk of the material presented is concerned with congenital heart disease, and again angiocardiography is emphasized. The brief section on rheumatic heart disease includes a discussion of the difficulties inherent in the evaluation of mitral valvular insufficiency in the presence of mitral stenosis. Left atrial puncture, recently shown to be quite valuable in this problem, is not mentioned.

Diseases of the aorta comprise the final section. Aortography is emphasized in the study of such problems, and methods for obtaining aortograms are described. Representative reproductions of x-rays amplify the text. In many instances diagrams are provided to clarify the pictures obtained using contrast substances.

The marked emphasis on congenital heart disease and angiocardiography has unbalanced the book somewhat. However, Dr. Cooley and Dr. Sloan are to be commended for producing a readable, concise volume which delineates the large contribution made by radiologists in the study of patients with cardiovascular disease. The book is recommended to all clinicians.

J. E. C.

The Treatment of Burns. By CURTIS P. ARTZ, M.D., F.A.C.S., Lt. Col., MC, USA (Ret.), and ERIC REISS, M.D. 250 pages; 16.5 × 25.5 cm. W. B. Saunders Company, Philadelphia. 1957. Price, $7.50.

This monograph of 250 pages, 199 illustrations and 105 figures on the treatment of burns more than fulfills the stated purposes of the authors which are twofold, viz.: (1) to furnish a guide for treatment in accordance with the present day knowledge of burns, and (2) to present information about certain practical details of management which are not discussed in scientific articles.

The reader's attention is especially directed to three chapters. The chapters on Initial Replacement Therapy, The Problem of Infection, and Metabolic Response and Nutrition present excellent discussions of basic problems which confront all physicians who treat burns of any magnitude.

Therapy of burns of special types and burns of specific areas are adequately covered by the authors. They have had the foresight not only to include a chapter on Practical Details of Burn Therapy, but have also briefly outlined a plan of treatment of burns in the event of mass disaster.

The material is well organized and well presented by the authors whose qualifications as outstanding authorities in the management of burns are well recognized.

This attractively printed and bound book is recommended to all who have more than a casual interest in the burn problem.

A. R. M., JR.

Rauwolfia: Botany, Pharmacognosy, Chemistry and Pharmacology. By ROBERT E. WOODSON, JR., Ph.D.; HEBER W. YOUNGKEN, Ph.D., Sc.D., Phm.D.; EMIL SCHLITTLER, Ph.D., and JURG A. SCHNEIDER, M.D., with a foreword by ARNOLD J. LEHMAN, M.D. 149 pages; 16 × 24 cm. Little, Brown & Co., Boston. 1957. Price, $5.50.

For untold centuries the roots and leaves of the shrub, *Rauwolfia serpentina* and related Rauwolfia species, known in India under a variety of folk names, have occupied a prominent place in Ayruvedic medicine as antidotes against the bites of reptiles, as a remedy for diarrhea and many other ailments, and in the treatment of

certain nervous disorders and disturbed mental states. But it has only been within recent years that the brilliant investigations of Indian scientists on the therapeutic usefulness, pharmacologic properties and chemical characteristics of various Rauwolfia preparations attracted the attention of clinicians and investigators in other countries and led to the introduction of many Rauwolfia preparations and certain of the more potent alkaloids, especially reserpine and structurally related ones, into the materia medica of most countries of the world.

The ability of certain Rauwolfia preparations to bring about a slow, gradual reduction in blood pressure in the hypertensive patient and the concomitant development of a calmative state (or "tranquilizing effect") in the agitated patient was especially striking to physicians. Indeed, we might say that Rauwolfia ushered in the era of "tranquilizing drugs" with the concept of a depressant drug with an effect different from sedation or hypnosis.

The present work is a comprehensive compilation by a team of experts of the botany, pharmacognosy, chemistry and pharmacology of Rauwolfia and its alkaloids. Each subject is treated in great detail in a separate chapter. Dr. Woodson considers the Genus Rauwolfia and its definition. The distribution, culture and propagation, and anatomy of the roots are thoroughly described. Dr. Youngken's chapter considers the physical characteristics and histology of many Rauwolfia species which make identification possible. Dr. Schlittler treats the extremely involved and complex chemistry of the Rauwolfia alkaloids in a most comprehensive and admirable way. Finally, Dr. Schneider, in an excellent chapter, summarizes the current knowledge of the pharmacology of Rauwolfia and its many alkaloids. All four authors have performed an excellent service in organizing and critically evaluating the scattered literature on the many Rauwolfia species and their derivatives—frequently in the face of seemingly insurmountable difficulties because of conflicting reports or studies involving preparations of unspecified, obscure, impure or uncertain Rauwolfia plant and alkaloidal preparations. A feature of each chapter which is certain to be found indispensable to all who use this book is the lengthy list of references and valuable bibliography.

With the publication of this book and recent extensive reviews on the pharmacology and chemistry of Rauwolfia and its alkaloids (Bein; Chatterjee and Pakrashi, 1956), our knowledge of this extremely fascinating class of drugs has been considerably enriched. This book is enthusiastically recommended to medical scientists and others who are interested in basic research in any of the areas of medicine in which Rauwolfia preparations are finding extensive use.

RAYMOND M. BURGISON, Ph.D.

Anatomie des Menschen. Ein Grundriss für Studierende und Ärzte, dargestellt nach systematischen, topographischen und praktischen Gesichtspunkten. I. Teil, Allgemeine Anatomie/Rücken/Bauch/Becken/Bein. 3. Auflage. By A. WALDEYER. (*Human Anatomy.* An Outline for Students and Physicians, Presented from Systematic, Topographic and Practical Viewpoints. Part I. General Anatomy, Back, Abdomen, Pelvis, Inferior Extremity. Third, newly revised edition.) 369 pages; 18 × 24.5 cm. Price, DM 38 ($9.50). If purchased with Part II: Head and Neck, Eye, Ear, Brain, Superior Extremity and Thorax, the total cost is DM 56, or $14.00. Walter de Gruyter & Co., Berlin. 1957.

This book and its approach to Human Anatomy are well described in the title. Rather than attempting to compress the vast amount of factual material of the larger texts into a relatively small volume, the author has sifted out the essentials and has enlivened them by emphasizing functional relationships and by reference to physiologic, pathologic and clinical considerations. Developmental and comparative anatomical facts are inserted where they are necessary to an understanding of the definitive form and its variations. Microscopic anatomy of the organs is presented

briefly and schematic diagrams of certain organs and systems are given to help clarify their functions. In this third edition the new or revised sections are those on the cell, muscle, connective and nervous tissues, blood, diaphragm, pancreas, kidney, source and organization of building materials and changes in the female genitalia during pregnancy. Several illustrations have been replaced by new ones.

The first one-fourth of the book is devoted to 8 general sections which introduce or review for the reader the various tissues and systems of the body. The remainder consists of a regional account of the Back (including the spinal medulla), Abdomen, Pelvis and Inferior Extremity. The author has assembled a great deal of basic anatomic information within this relatively small book. Those who read German moderately well should have no difficulty with the clear, uncomplicated style of the author.

The illustrations are well executed and beautifully reproduced on fine quality paper. Many are purely schematic or modified and schematized from other sources. The half-tone reproductions of original drawings, done presumably from the specimen, have a "stiffness" or stylized quality about them which, while imparting to them a fresh crispness, at the same time suggests a meticulously exact drawing of a model rather than of an actual specimen. This does not detract from their beauty or usefulness, however, for with few exceptions (notably the representation of endopelvic fascias) structures and their relationships are correctly delineated.

Dr. Waldeyer does not employ the newly-adopted Nomina Anatomica (Paris, 1955) but uses the older J.N.A. of the German Nomenklature-Kommission about which many English and American and some German, Dutch and Scandinavian anatomists have expressed dissatisfaction. Both systems, however, are largely based upon the familiar B.N.A. nomenclature. In numerous cases alternate terms and eponyms are given in brackets and parentheses, and the vernacular terminology is used in the accompanying text along with the Latin terms. The beginner or any student, if his knowledge of German is limited, will be somewhat annoyed by inconsistencies in the labelling of figures. Some are labelled entirely in German, some entirely in the Latin form of the J.N.A and others by an admixture of both.

The book is sufficiently detailed to be useful in courses of Anatomy for technicians, occupational therapists, physiotherapists or nurses, especially where dissections are prepared and demonstrated by a prosector. In graduate and freshman medical courses it might be used along with, but not as a substitute for the more detailed anatomical textbooks and atlases. The practising physician who wishes to refresh his memory of a region by a brief survey which covers description, important relationships and some functional considerations together with good illustrations may find this book well suited to his needs.

VERNON E. KRAHL, Ph.D.

The Give and Take in Hospitals: A Study of Human Organization. By TEMPLE BURLING, M.D., EDITH M. LENTZ, Ph.D., and ROBERT N. WILSON, Ph.D. 355 pages; 14 × 21 cm. G. P. Putnam's Sons, New York. 1956. Price, $4.75.

This book is the report of a study made through the American Hospital Association by the New York State School of Industrial and Labor Relations at Cornell University. Using a social-anthropological approach the investigators, a practicing psychiatrist and two social scientists, studied all levels of hospital personnel from board members to laborers in an effort to understand the hospital through the interpersonal relationships of the occupational groups involved. Six representative general hospitals were studied. The social scientists were purposely chosen from outside the hospital field so the study could be truly objective. Their disinterested observations highlight many aspects of staff interpersonal relationships that might have been overlooked by investigators more closely identified with the setting.

Four topics are considered in the major divisions of the volume: Hospitals and the American Scene, The Hospital Power Structure, A Study of Some Hospital Occupational Groups, and Some Hospital Departments in Action. Basic to the understanding of any hospital is an awareness of the historical development of institutional care of the sick in relation to the development of medicine and the evolution of the community's acceptance of responsibility in planning to meet health needs, for these determine the purpose and goal of the hospital. Within the hospital personnel groups are areas of conflict and dissatisfactions, status patterns and motivations, all of which must be synthesized into an organization functioning coöperatively toward the common goal of meeting patient needs. The investigators have assayed to select the factors which appear most dynamic in dissipating or integrating this effort.

Of particular interest to physicians, who are charged with giving the best possible medical care, and administrators, who have the responsibility of providing the setting in which this care can be given, is Part Two which discusses the hospital power structure. Here the investigators demonstrate how "the hospital and medical staff impinge upon one another at every point. Each sustains each and is vital to the survival of the other."

Occupational groups and hospital departments are considered in terms of their characteristics as groups and the significance of these characteristics to the operations of departments. It is only with this awareness of the parts that comprise the whole that departments can be fully understood and maximally effective.

The book ends with a chapter on "Communication Needs in a Growing Institution." The growth of hospitals in size and complexity and the rise of the many specialties point to the need for an acceptance of the rôles of others and a willingness to share with them to make the efforts of any one group fully productive.

J. M. D.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Accidents in Childhood: Facts as a Basis for Prevention. Report of an Advisory Group. World Health Organization Technical Report Series No. 118. 40 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Allergy Recipes. 64 pages; 21.5 × 14 cm. (paper-bound). 1957. The American Dietetic Association, Chicago. Price, Single copy, 50¢; lots of 10, $4.50; lots of 50, $20.00.

Biochemical Disorders in Human Disease. Edited by R. H. S. THOMPSON, M.A., D.M., Professor of Chemical Pathology, University of London (Guy's Hospital Medical School); and E. J. KING, Ph.D., F.Sc., F.R.I.C., Professor of Chemical Pathology, University of London (Postgraduate Medical School). 843 pages; 25 × 16 cm. 1957. Academic Press, Inc., New York. Price, $12.60.

Bronchopulmonary Diseases: Basic Aspects, Diagnosis and Treatment. By 142 authors; edited by EMIL A. NACLERIO, M.D., Chief of the Thoracic Surgical Services, Harlem and Columbus Hospitals, New York; foreword by RICHARD H. OVERHOLT, M.D., Director, Overholt Thoracic Clinic, Boston, etc. 956 pages; 28 × 20.5 cm. 1957. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $24.00.

The Caricature of Love: A Discussion of Social, Psychiatric, and Literary Manifestations of Pathologic Sexuality. By HERVEY CLECKLEY, M.D., Clinical Professor of Psychiatry and Neurology, Medical College of Georgia, etc. 319 pages; 23.5 × 15.5 cm. 1957. The Ronald Press Company, New York. Price, $6.50.

Cirrhose und Narbenleber: Entstehung, Klinik und Therapie. By PROF. DR. MED. HEINZ KALK. 162 pages; 24.5 × 16 cm. 1957. Ferdinand Enke Verlag, Stuttgart. Price, Geheftet DM 22.–; ganzleinen DM 24.50.

Clinical Physiology: The Functional Pathology of Disease. Edited by ARTHUR GROLLMAN, M.D., Ph.D., F.A.C.P., Professor and Chairman of the Department of Experimental Medicine, University of Texas Southwestern Medical School, Dallas. 854 pages; 24 × 16 cm. 1957. The Blakiston Division, McGraw-Hill Book Company, Inc., New York. Price, $12.50.

The Diagnosis and Treatment of Pulmonary Tuberculosis. 2nd Ed. By PAUL DUFAULT, M.D., Medical Director of the Rutland State Sanatorium, Massachusetts Department of Public Health; with a chapter on Pathology by A. REYNOLDS CRANE, M.D., Professor of Pathology, University of Pennsylvania School of Medicine, etc.; and a chapter on Pulmonary Function by OSCAR FEINSILVER, M.D., Senior Visiting Physician at St. Vincent Hospital, Worcester, Massachusetts, etc. 426 pages; 20.5 × 13.5 cm. 1957. Lea & Febiger, Philadelphia. Price, $9.00.

Expert Committee on Biological Standardization: Tenth Report. World Health Organization Technical Report Series No. 127. 35 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Food Facts Talk Back: Food Information—Fallacies and Facts. 32 pages; 23 × 15 cm. (paper-bound). 1957. The American Dietetic Association, Chicago. Price, 50¢ per copy; $2.25 for 5 copies; $4.00 for 10 copies; $17.50 for 50 copies.

Gastro-intestinal Obstruction. By MEYER O. CANTOR, M.D., M.S., F.A.C.S., Associate Attending Surgeon, Grace Hospital, etc.; and ROLAND P. REYNOLDS, M.D., F.A.C.S., Chief of Surgery, Grace Hospital; contributors: CLIFFORD D. BENSON, M.D., F.A.C.S., Associate Professor of Surgery, Wayne University, etc.; ROBERT E. L. BERRY, M.D., F.A.C.S., Associate Professor of Surgery, University of Michigan; and WILLIAM A. HUDSON, M.D., M.S., F.A.C.S., Associate Professor Surgery (retired), Wayne University, etc. 565 pages; 27 × 19.5 cm. 1957. The Williams & Wilkins Company, Baltimore. Price, $18.00.

Heredo-retinopathia Congenitalis: Monohybrida Recessiva Autosomalis. A Genetical-Statistical Study. By CARL HENRY ALSTRÖM, Laboratory No. 2 for Human Genetics, The Psychiatric Clinic of the Caroline Institute, Stockholm; in clinical collaboration with OLOF OLSON, The State Institute for the Blind, Tomteboda, Stockholm. 178 pages; 24 × 18 cm. (paper-bound). 1957. Berlingska Boktryckeriet, Lund.

Neuropharmacology: Transactions of the Third Conference, May 21, 22, and 23, 1956, Princeton, N. J. Edited by HAROLD A. ABRAMSON, M.D., Research Psychiatrist, The Biological Laboratory, Cold Spring Harbor, etc. 381 pages; 23.5 × 16 cm. 1957. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $4.50.

Oligophrenia in Combination with Congenital Ichthyosis and Spastic Disorders: A Clinical and Genetic Study. (Acta Psychiatrica et Neurologica Scandinavica

Supplementum 113, Volumen 32, 1957.) By TORSTEN SJÖGREN and TAGE LARSSON, with the assistance of GÖTA PETERSSON. 108 pages; 24.5 × 16.5 cm. (paper-bound). 1957. Ejnar Munksgaard, Copenhagen. Price, d. kr. 33.–

The Physiology of Induced Hypothermia: Proceedings of a Symposium, 28–29 October 1955, Convened by The Division of Medical Sciences, National Academy of Sciences—National Research Council, with the sponsorship of The United States Army, Navy, and Air Force. By ROBERT D. DRIPPS, M.D., Chairman and Editor. 447 pages; 25.5 × 18 cm. 1956. Publication 451, National Academy of Sciences—National Research Council, Washington, D. C. Price, $3.50.

Physiology of Prematurity: Transactions of the First Conference, March 21, 22, and 23, 1956, Princeton, N. J. Edited by JONATHAN T. LANMAN, M.D., Department of Pediatrics, New York University-Bellevue Medical Center, New York, N. Y. 151 pages; 24 × 16 cm. 1957. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $3.25.

Practical Forensic Medicine. By FRANCIS E. CAMPS, M.D., Reader in Forensic Medicine (University of London) at The London Hospital Medical College; and W. B. PURCHASE, C.B.E., M.C., M.B., D.P.H., Barrister-at-Law, etc. 541 pages; 24 × 15.5 cm. (leather-bound). 1957. The Macmillan Company, New York. Price, $13.50.

Prevention of Chronic Illness. Volume I of *Chronic Illness in The United States.* Based on the work of the COMMISSION ON CHRONIC ILLNESS. 338 pages; 24 × 16 cm. 1957. Published for The Commonwealth Fund by Harvard University Press, Cambridge. Price, $6.00.

Prevention of Rheumatic Fever: Second Report of the Expert Committee on Rheumatic Diseases. World Health Organization Technical Report Series No. 126. 27 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 50¢.

Rôle of Hospitals in Programmes of Community Health Protection: First Report of the Expert Committee on Organization of Medical Care. World Health Organization Technical Report Series No. 122. 34 pages; 24 × 16 cm. 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

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